I3Y-MC-JPCG(b) Clinical Protocol

A Randomized, Open-Label, Phase 2 Study of Abemaciclib plus Tamoxifen or Abemaciclib Alone, in Women with Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer.

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Approval Date: 29-Jan-2019

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A Randomized, Open-Label, Phase 2 Study of Abemaciclib plus Tamoxifen or Abemaciclib Alone, in Women with Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer

Abemaciclib (LY2835219)

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1. Synopsis

Protocol Title: A Randomized, Open-Label, Phase 2 Study of Abemaciclib plus Tamoxifen or Abemaciclib Alone, in Women with Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer.

Rationale: This Phase 2 study is a multicenter, randomized, open-label study to evaluate the efficacy and tolerability of abemaciclib alone or in combination with endocrine therapy as a treatment for patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer (mBC) who have progressed on or after prior endocrine therapies. Patients must have received prior treatment with at least 2 chemotherapy regimens, of which at least 1 but no more than 2 regimens have been administered in the metastatic setting. The currently approved standards of care offered to this population are predominantly chemotherapies associated with treatment-limiting toxicity. Abemaciclib monotherapy and in combination with endocrine therapy has demonstrated clinical activity and an acceptable tolerability profile in patients with mBC. This Phase 2 study will evaluate and compare the efficacy and tolerability of abemaciclib monotherapy at 2 dose levels and abemaciclib in combination with endocrine therapy for patients with previously treated HR+, HER2- mBC.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the efficacy, in terms of PFS, in patients with metastatic breast cancer for: • Abemaciclib 150 mg Q12H plus tamoxifen • Abemaciclib 150 mg Q12H • Abemaciclib 200 mg Q12H plus primary prophylactic loperamide	PFS (objective progression or death), as determined by investigator assessment per RECIST v1.1
Secondary	
To evaluate the efficacy of abemaciclib monotherapy and in combination with tamoxifen, in terms of ORR, DoR, and OS	Efficacy endpoints will include: • ORR (CR + PR) based on tumor assessment using RECIST v1.1 • DoR (CR+ PR) per RECIST v1.1 • OS
To assess the safety profile of abemaciclib monotherapy and in combination with tamoxifen	Safety endpoints will include but are not limited to the following: • TEAEs, SAEs, and hospitalizations • Clinical laboratory tests, vital signs, and physical examinations
To characterize the PK of abemaciclib and its metabolites; in addition to tamoxifen and its active metabolite endoxifen	PK parameters for abemaciclib and tamoxifen
To compare self-reported pain, pain interference, symptom burden, health status, and overall quality of life	Compare self-reported pain, pain interference, symptom burden, health status, and quality of life using the mBPI-sf and EORTC QLQ-C30

Abbreviations: CR = complete response; DoR = duration of response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; mBPI-sf = modified Brief Pain Inventory-short form; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; Q12H = every 12 hours; RECIST v 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design: I3Y-MC-JPCG (JPCG) is a Phase 2, multicenter, randomized, open-label study of abemaciclib plus tamoxifen or abemaciclib alone, in women with previously treated HR+, HER2- mBC.

Number of Patients: The study will screen approximately 270 patients, and approximately 225 patients with HR+, HER2- mBC will be enrolled in the study and randomized 1:1:1 to one of the three treatment arms. Treatment will be given in an outpatient setting and will continue until evidence of disease progression or other discontinuation criteria are met.

Treatment Arms and Duration:

	Dose and Schedule (Q28 Days)	
Arm	**Abemaciclib Dose**	**Tamoxifen Dose (Arm A only)**
A	150 mg Q12H	20 mg QD
B	150 mg Q12H	--
C[a]	200 mg Q12H	--

Abbreviations: Q = every; Q12H = every 12 hours; QD = every 24 hours.

a Arm C only. During Cycle 1, loperamide 2 mg will be administered orally, prophylactically with the first dose of abemaciclib daily. During Cycle 2 and beyond, loperamide will be administered either as prophylaxis or supportive care based on investigator's discretion and/or if clinically indicated.

2. Schedule of Activities

Table JPCG.1. Baseline Schedule of Activities

Relative Day Prior to Day 1 of Cycle 1 (Day -1)	≤28	≤14	≤7	Comments
Procedure				
Informed consent	X			Informed consent form signed (prior to performance of any protocol-specific tests/procedures).
Serum pregnancy test			X	Women with childbearing potential must have a negative serum pregnancy test within 7 days of the first dose of study drug (i.e. Day -7 to Day -1).
Medical history		X		Including alcohol/tobacco use and other relevant habits assessments. Includes prior anticancer therapy.
Physical exam, vital signs, height, and weight		X		Vital signs include blood pressure, pulse, respiratory rate, and temperature.
ECOG performance status		X		
Concomitant medications		X		Any current medications.
CTCAE version 4.0 grading (preexisting conditions)		X		
Tumor measurement (visible lesions)	X			Photography of visible lesions (such as skin lesions) with ruler required, if applicable.
Radiological tumor assessment	X			Imaging studies (CT scan or MRI) are performed locally (Day -28 to Day -1) at baseline. It is recommended that CT imaging of the chest, abdomen and pelvis be performed with IV contrast, whenever possible. For patients with known hypersensitivity to CT contrast material, a CT scan of the chest without contrast and Gd-MRI of the abdomen/pelvis are encouraged.
Bone scintigraphy (preferred) or PET scan or PET component of PET/CT scan	X			One of these studies (Bone scintigraphy [preferred], PET scan, or PET component of PET/CT scan) of the whole body is performed locally at baseline. An available prior bone scintigraphy or PET scan performed as part of routine clinical care within 45 days before Cycle 1 Day 1 is acceptable.

Baseline Schedule of Activities

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
Procedure				
X-ray or CT scan with bone windows or MRI	X			Required only for patients with nonmeasurable bone disease identified on the baseline bone scintigraphy, PET, or PET component of PET/CT. One or more of these studies (X-ray, CT scan with bone windows, or MRI) is performed locally (Day -28 to Day -1) at baseline. All bone lesions will be evaluated by focused studies to enable serial assessment.
MRI of brain	X			Required for all patients. Performed locally (Day -28 to Day -1) at baseline.
ECG		X		ECGs will be performed locally (Day -14 to Day -1). This baseline ECG (no replicates required) is required to establish eligibility for this study.
mBPI-sf and EORTC QLQ-C30		X		Patient completes prior to extensive interaction at site.
Central hematology		X		Enrollment and treatment decisions may be based upon local laboratory results. If local laboratory results are used for this purpose, a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory results will not be considered protocol deviations.
Central chemistry		X		Enrollment and treatment decisions may be based upon local laboratory results. If local laboratory results are used for this purpose, a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory results will not be considered protocol deviations.

Abbreviations: CT = computerized tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; Gd = gadolinium; IV = intravenous; mBPI-sf = modified Brief Pain Inventory-short form; MRI = magnetic resonance imaging; PET = positron emission tomography.

Table JPCG.2. On-Study-Treatment Schedule of Activities

	Cycle 1		Cycle 2		Cycle 3 and beyond (per instructions)	
Day within cycle (28 days = 1 cycle)	**1**	**15**	**1**	**15**	**1**	
Procedure						**Comments**
Physical examination	X	X	X		X	Including weight and vital signs (temperature, blood pressure, pulse rate, respiration rate). May be performed up to 3 days prior to Day 1 of each cycle, as well as up to 3 days prior to Day 15 of Cycle 1.
Concomitant medication	X	X	X		X	Including concomitant medication at study start and, throughout study as needed.
Adverse event collection	X	X	X		X	Adverse event grading using CTCAE Version 4.0 will be performed throughout the study. All drug- or procedure-related AEs and SAEs should be followed until they resolve, are no longer considered to be drug- or procedure-related, become stable or return to baseline, the patient starts a new therapy, the patient dies, or the patient becomes lost to follow-up.
ECOG performance status	X	X	X		X	May be performed up to 3 days prior to Day 1 of each cycle, as well as up to 3 days prior to Day 15 of Cycle 1.
Radiological tumor assessment					X	Performed locally. Imaging studies are performed every 8 weeks (-7 days) from the first dose of study therapy and within 14 days of clinical progression. The same method of imaging used at baseline should be used for each subsequent assessment.
Bone scintigraphy (preferred) or PET scan or PET component of PET/CT scan					X	Required only for patients with nonmeasurable bone disease identified at baseline or if clinically indicated. Postbaseline bone scintigraphy or PET should be performed every 24 weeks (-7 days) from first dose of study therapy. Importantly, RECIST v1.1 emphasizes that bone scintigraphy is not adequate to measure bone lesions; however, bone scintigraphy can be used to confirm the presence or disappearance of bone lesions.

On-Study-Treatment Schedule of Activities

	Cycle 1		Cycle 2		Cycle 3 and beyond (per instructions)	
Day within cycle (28 days = 1 cycle)	**1**	**15**	**1**	**15**	**1**	
Procedure						**Comments**
X-ray or CT scan with bone windows or MRI					X	Required only for patients with nonmeasurable bone disease identified at baseline. One or more of these studies (X-ray, CT scan with bone windows, or MRI), identical to the study obtained at baseline, is performed locally every 8 weeks (-7 days) from first dose of study therapy and within 14 days of clinical progression. For patients with new lesions identified by postbaseline bone scintigraphy, targeted assessment by X-ray, CT scan with bone windows, or MRI will be performed to confirm findings.
Tumor measurement (visible lesions)					X	Skin lesions identified at baseline require repeat photographic images every 8 weeks (-7 days) from the first dose of study therapy and within 14 days of clinical progression. Photographic images may be taken more frequently based upon the discretion of the investigator or following the identification of new skin lesions postbaseline.
Patient diary dispensing/collection	X	X	X	X	X	Patient diaries should be completed by the patient during cycles 1, 2, and 3.
Administer mBPI-sf and EORTC QLQ-C30 questionnaires	X	X	X		X	To be administered prior to extensive interaction with site staff at each visit when administered. Continue administration at every cycle through Cycle 7 Day 1 and then administer at every other cycle starting with Cycle 9 and beyond.
Administer abemaciclib	X					Administer prescribed dose orally every 12 hours on Days 1 through 28 of every cycle. Patients may take study drug with or without meals.

On-Study-Treatment Schedule of Activities

	Cycle 1		Cycle 2		Cycle 3 and beyond (per instructions)	
Day within cycle (28 days = 1 cycle)	**1**	**15**	**1**	**15**	**1**	
Procedure						**Comments**
Administer tamoxifen	X					**Arm A patients only.** Administer prescribed dose orally every 24 hours on Days 1 through 28 of every cycle.
Administer loperamide	X					**Only patients in Arm C should take loperamide prophylactically** (daily during Cycle 1 with their first dose of abemaciclib). Patients in Arms A and B should only take loperamide if the patient experiences diarrhea and requires treatment. See Section 7.4.1.1.1.3 for additional information.
Sample collection						
Central hematology	X	X	X	X	X	Central hematology labs can be drawn up to 3 days prior to Day 1 of each cycle, as well as up to 3 days prior to Day 15 of Cycles 1 and 2. Additional local hematology labs may be drawn for treatment adjustment and patient management purposes. Duplicate central labs should be submitted for assessment. Discrepancies between local and central laboratory results will not be considered protocol deviations.
Central chemistry	X	X	X	X	X	Central chemistry labs can be drawn up to 3 days prior to Day 1 of each cycle, as well as up to 3 days prior to Day 15 of Cycles 1 and 2. Additional local chemistry labs may be drawn for treatment adjustment and patient management purposes. Duplicate central labs should be submitted for assessment. Discrepancies between local and central laboratory results will not be considered protocol deviations.
Serum pregnancy test			X		X	Required only for women of child bearing potential if mandated by local country regulations. Additional serum pregnancy tests performed locally, on Day 1 (or up to 3 days before Day 1) of every cycle beginning with Cycle 2.
Pharmacokinetics	X	X	X	X	X	See Appendix 4 for details on sample collection
Pharmacogenetic blood sample	X					

On-Study-Treatment Schedule of Activities

	Cycle 1		Cycle 2		Cycle 3 and beyond (per instructions)	
Day within cycle (28 days = 1 cycle)	**1**	**15**	**1**	**15**	**1**	
Procedure						**Comments**
Biomarker plasma sample	X		X		X	Collect at Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1. See Appendix 4 for details on timing for sample collection
Archived tumor tissue	X					Formalin-fixed paraffin-embedded (FFPE) tumor sample must be requested after study eligibility is confirmed.

Abbreviations: AE = adverse event; CT = computerized tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; mBPI-sf = modified Brief Pain Inventory-short form; MRI = magnetic resonance imaging; PET = positron emission tomography; RECIST v 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SAE = serious adverse event.

Table JPCG.3. Post-Treatment Follow-Up Schedule of Activities

	Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	
Visit	**801**	**802-8XX**	
Procedure			**Comments**
Physical examination	X		Including weight and vital signs (temperature, blood pressure, pulse rate, respiration rate).
Concomitant medication	X		
Adverse event collection	X		CTCAE Version 4.0. After Visit 801, only study protocol or drug-related events are reported. If a patient has an ongoing AE or SAE possibly related to study drug (for instance, abnormal electrolytes), the patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Any subsequent follow-up(s) for AEs will be no more than 30 days ± 7 in duration.
ECOG performance status	X		
Radiological tumor assessment	X	X	Not required if objective progressive disease is documented while on treatment. Continue to conduct tumor assessment every 8 weeks (-7 days) until patient has objective disease progression or until primary PFS analysis. After the patient has objective disease progression, radiologic tests are no longer required and the patient will continue with postdiscontinuation follow-up for a minimum of every 90 days until death or study completion.
Bone scintigraphy (preferred) or PET Scan or PET component of PET/CT Scan	X	X	Not required if objective progressive disease is documented while on treatment. Continue to evaluate repeat bone scans approximately every 24 weeks until objective disease progression or primary PFS analysis.
X-ray or CT scan with bone windows or MRI	X	X	Only for patients with nonmeasurable bone disease previously identified. Not required if objective progressive disease is documented while on treatment. Continue to conduct tumor assessment every 8 weeks (-7 days) until patient has objective disease progression or until primary PFS analysis. After the patient has objective disease progression, radiologic tests are no longer required and the patient will continue with postdiscontinuation follow-up for a minimum of every 90 days until death or study completion.

Post-Treatment Follow-Up Schedule of Activities

	Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	
Visit	**801**	**802-8XX**	
Procedure			**Comments**
Tumor measurement (visible lesions)	X	X	Not required if objective progressive disease is documented while on treatment. Continue to conduct tumor assessment every 8 weeks (-7 days) until patient has objective disease progression or until primary PFS analysis. After the patient has objective disease progression, tumor assessments are no longer required and the patient will continue with postdiscontinuation follow-up for a minimum of every 90 days until death or study completion.
Survival information	X	X	Survival information may be collected by contacting the patient or family directly (for example, via telephone) if no procedures are required. This should be collected at minimum every 90 days if no other procedures are performed.
Collection of post-study-treatment anticancer therapy information	X	X	Perform for a minimum of every 90 days until death or study completion.
Central hematology	X		For sample collection, see Appendix 3.
Central chemistry	X		
Serum pregnancy test	X		Required only for women of child bearing potential if mandated by local country regulations. Serum pregnancy test performed locally at short-term follow up visit.
Biomarker plasma sample	X		Collect at time of discontinuation.
Administer mBPI and EORTC QLQ-C30 questionnaires	X		Collect prior to extensive site interaction.

Abbreviations: AE = adverse event; CT = computerized tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; mBPI-sf = modified Brief Pain Inventory-short form; MRI = magnetic resonance imaging; PET = positron emission tomography; SAE = serious adverse event.

a Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (± 7 days). No follow-up procedures will be performed for a patient who withdraws informed consent unless she has explicitly provided permission and consent.

b Long-term follow up begins the day after short-term follow up is completed and continues every 90 days until the patient's death or overall study completion.

Table JPCG.4. Continued Access Schedule of Activities

Visit	Study Treatment	Follow-Up[a]	
	501-5XX	901	
Procedure[b]			**Comments**
Adverse event collection	X	X	CTCAE Version 4.0. Assessments to be conducted with each collection and dispensing of study drug (every 28 days) from Visits 501-5XX.
Administer study drug	X		

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

a Continued access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days (± 7 days). No follow-up will be performed for a patient who withdraws informed consent unless she has explicitly provided permission and consent.

b Efficacy assessments will be done at the investigator's discretion based on the standard of care.

3. Introduction

3.1. Study Rationale

Study I3Y-MC-JPCG (JPCG) is a Phase 2 study for patients with previously treated hormone receptor-positive (HR+)/ human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (mBC) who have progressed on or after prior endocrine therapy and have previously received treatment with at least 2 chemotherapy regimens, of which at least 1 but no more than 2 regimens have been administered in the metastatic setting. The study will evaluate the potential to enhance the risk/benefit profile of abemaciclib monotherapy, either administered at the maximum recommended single-agent dose of 200 mg every 12 hours (Q12H) with primary prophylactic antidiarrheal medication, at a lower dose of abemaciclib monotherapy, or in combination with endocrine therapy in approximately 225 patients.

3.2. Background

Breast cancer is the most commonly diagnosed malignancy in women, and the second leading cause of cancer deaths in women in the United States (US), with 231,840 new cases of breast cancer and 40,290 deaths estimated in 2015 (ACS 2015). Worldwide, breast cancer is the most frequent cancer among women and is a major cause of cancer-related deaths. It is estimated that more than 1.67 million new cases of breast cancer occurred worldwide in women in 2012 (Ferlay et al. 2015). According to the National Cancer Institute Surveillance, Epidemiology, and End Results database, the 5-year survival rate for women with Stage IV breast cancer is 26% (Howlader et al. 2015).

The HR+/HER2- subtype is the most prevalent of breast cancer subtypes and accounts for approximately 70% of all breast cancers (Howlader et al. 2014). Despite the availability of endocrine therapies for the treatment of HR+ mBC, most patients ultimately relapse and develop acquired endocrine resistance. Patients are generally treated with multiple lines of endocrine therapy with the benefit progressively diminishing as resistance develops. When endocrine therapy is no longer an appropriate therapeutic option, sequential single-agent cytotoxic chemotherapy becomes the standard of care for these patients (Swallow et al 2014). Hormone receptor-positive mBC is incurable and therefore considered a serious and life-threatening disease, with a median overall survival (OS) of only 2 to 3 years (Cardoso et al. 2012). In addition, after progressing on 1 to 2 cytotoxic chemotherapy regimens in the metastatic setting, life expectancy is only 12 to 15 months (O'Shaughnessy et al. 2002; Cortes et al. 2011; Krop et al. 2014; Kaufman et al. 2015). There is a significant unmet medical need for the development of novel agents for the treatment of HR+ mBC in order to improve OS, delay disease progression, minimize breast cancer-related symptoms, and/or delay the need for additional chemotherapy.

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for proper regulation of cell proliferation (Sherr 1996; Ortega et al. 2002). Cyclin-dependent kinase (CDK) 4 and CDK 6 participate in a complex with the D-type cyclins to initiate progression through the G1 restriction point. The CDK 4 and CDK 6 – cyclin D complex regulates the G1

restriction point through phosphorylation and inactivation of the retinoblastoma (Rb) tumor suppressor protein, thereby promoting S phase entry (Sherr 1996; Ortega et al. 2002). Alterations in this pathway occur frequently in human cancers and include 1) loss of functional CDK inhibitors through deletion or epigenetic silencing, 2) activating mutations and/or overexpression of CDK 4 and CDK 6 or the D-type cyclins, and 3) loss of functional Rb through mutation or deletion (Malumbres and Barbacid 2001). Except for tumors with functional loss of Rb, which functions downstream of the CDK 4 and CDK 6-cyclin D complex, most cancers are potentially sensitive to pharmacologic inhibition of CDK 4 and CDK 6. From a therapeutic standpoint, the goal of inhibiting CDK 4 and CDK 6 in HR+ breast cancers is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

Many HR+ breast cancers demonstrate overexpression of cyclin D1, which interacts directly with the estrogen receptor (ER) to activate ER target genes (Neuman et al. 1997; Zwijsen et al. 1997, 1998). Cyclin D also interacts directly with CDK 4 and CDK 6 in an active protein complex that promotes cell proliferation. Furthermore, endocrine resistance in HR+ breast cancer is associated with the deregulation of proliferation-associated genes that are regulated by CDK 4 and CDK 6 (Asghar et al. 2015). In addition, 4-hydroxytamoxifen significantly inhibited cyclin D1-mediated activation of the estrogen receptor (Neuman et al. 1997). Consequently, CDK 4 and CDK 6 inhibition represents a potential therapeutic target for HR+ breast cancer and dual inhibition of cyclin D1 (by inhibition of CDK 4 and CDK 6) and ER may enhance the prevention of cell cycle progression and overcome resistance to endocrine therapy.

Abemaciclib is a potent and selective small molecule inhibitor of cyclin D-dependent kinases CDK 4 and CDK 6, showing some preference for inhibiting cyclin D1/CDK 4 relative to CDK 6 in enzymatic assays. Abemaciclib prevents Rb phosphorylation, blocking progression from G1 into S phase of the cell cycle, leading to suppression of tumor growth in preclinical models. Abemaciclib demonstrates suitable physical and pharmacokinetic (PK) properties, an acceptable toxicity profile in nonclinical species, and antitumor activity in multiple mouse models of human cancer. Cell-based studies in breast cancer models have demonstrated that abemaciclib inhibits CDK 4 and CDK 6 to induce G1 arrest specifically in cell lines with functional Rb versus lines which lack functional Rb. Additional cell-based studies, which evaluated in vitro growth inhibition across a diverse panel of 46 breast cell lines representing the known molecular subgroups of breast cancer, indicated that sensitivity to CDK 4 and CDK 6 inhibition was greater in ER+ lines with luminal histology. In ER+ breast cancer cell lines, sustained target inhibition with single-agent abemaciclib produces a continuous cell cycle arrest which over time results in a loss of replicative potential by inducing senescence or death through apoptosis. In vivo, abemaciclib monotherapy dosed daily without interruption at clinically relevant concentrations in xenograft models resulted in reduction of tumor size. Studies in mice bearing ER+ breast cancer xenografts with abemaciclib and 4-hydroxytamoxifen showed that the combination of the 2 agents improved the durability of the antitumor responses when compared to either abemaciclib or 4- hydroxytamoxifen alone.

In clinical trials, abemaciclib has induced partial responses and prolonged stable disease for patients with HR+ breast cancer (Patnaik et al. 2014; Goetz et al. 2015; Tolaney et al. 2015). In

study I3Y-MC-JPBA (JPBA), clinical activity of abemaciclib monotherapy and in combination with endocrine therapy was observed in patients with pretreated HR+ breast cancer across dose levels. In a cohort of 36 HR+ patients in Study JPBA the overall response rate was 33%. The tumors in 26% (7/27) of patients receiving abemaciclib monotherapy responded and 56% (5/9) of patients who received concomitant endocrine therapy with abemaciclib experienced a tumor response. The impact of starting dose (150 mg [n=25] or 200 mg [n=22]) and continuation of previous endocrine therapy (9 of 36 patients) was unclear due to the small sample size and nonrandomized design. However, similar response rates were observed at both doses and patients continuing endocrine therapy remained progression free longer than those receiving monotherapy (mPFS of 24 months vs mPFS of 5.2 months). Additionally, abemaciclib in combination with multiple endocrine therapies demonstrated early evidence of activity against HR+ mBC in the ongoing Phase 1b Study I3Y-MC-JPBH (Goetz et al. 2015). One of the combinations studied in Study JPBH was abemaciclib plus tamoxifen. Safety and tolerability for this combination are described in more detail in Section 5.5.

This Phase 2 study I3Y-MC-JPCG (JPCG) will evaluate the potential to enhance the risk/benefit profile of abemaciclib in women with previously treated HR+, HER2- mBC, either administered in combination with endocrine therapy, at the recommended single-agent dose with primary prophylactic antidiarrheal medication, or at a lower starting single-agent dose.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of abemaciclib may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to abemaciclib may be found in Section 7 (Development Core Safety Information [DCSI]) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study may be found in Section 6 (Effects in Humans) of the IB.

More detailed information about the known and expected benefits and risks of tamoxifen may be found in the following: Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

4. Objectives and Endpoints

Table JPCG.5 shows the objectives and endpoints of the study.

Table JPCG.5. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy, in terms of PFS, in patients with metastatic breast cancer for: • Abemaciclib 150 mg Q12H plus tamoxifen • Abemaciclib 150 mg Q12H • Abemaciclib 200 mg Q12H plus primary prophylactic loperamide	PFS (objective progression or death), as determined by investigator assessment per RECIST v1.1
Secondary	
To evaluate the efficacy of abemaciclib, monotherapy and in combination with tamoxifen, in terms of ORR, DoR, and OS	Efficacy endpoints will include: • ORR (CR + PR) based on tumor assessment using RECIST v1.1 • DoR (CR+ PR) per RECIST v1.1 • OS
To assess the safety profile of abemaciclib monotherapy and in combination with tamoxifen	Safety endpoints will include but are not limited to the following: • TEAEs, SAEs, and hospitalizations • Clinical laboratory tests, vital signs, and physical examinations
To characterize the PK of abemaciclib and its metabolites; in addition to tamoxifen and its active metabolite endoxifen	PK parameters for abemaciclib and tamoxifen
To compare self-reported pain, pain interference, symptom burden, health status, and overall quality of life	Compare self-reported pain, pain interference, symptom burden, health status, and quality of life using the mBPI-sf and EORTC QLQ-C30
Tertiary/Exploratory	
To evaluate the associations between biomarkers and clinical outcomes	Efficacy outcomes such as ORR, PFS, and/or OS
To evaluate the relationship between abemaciclib and tamoxifen exposure and response	Drug exposure and efficacy outcomes such as PFS, OS and safety outcomes such as neutropenia and diarrhea

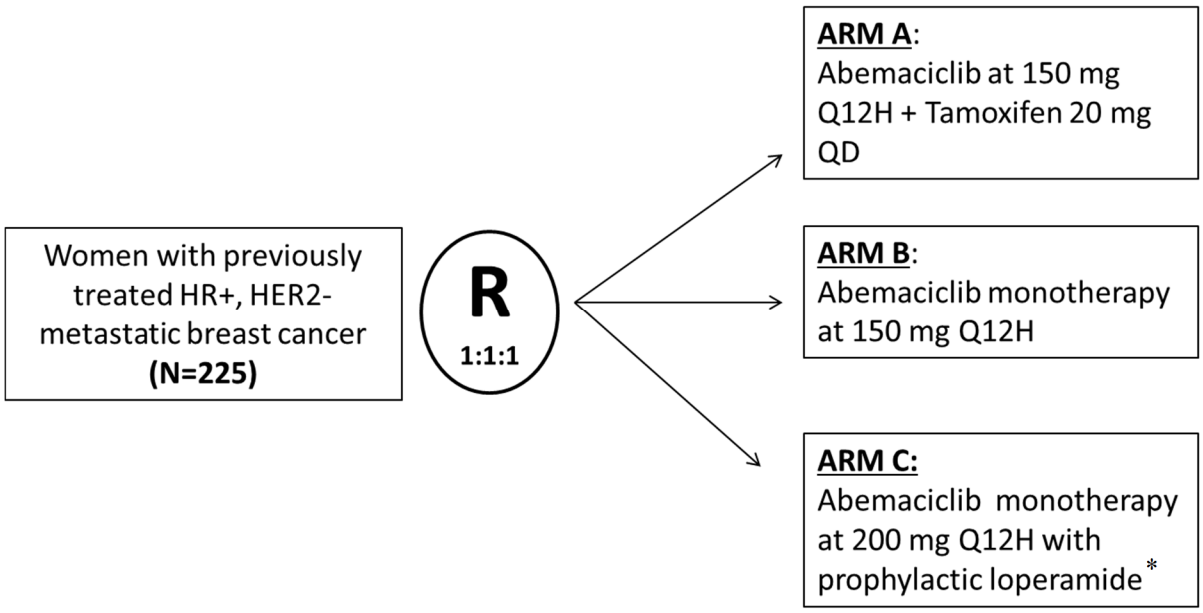
Abbreviations: CR = complete response; DoR = duration of response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; mBPI-sf = modified Brief Pain Inventory-short form; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; Q12H = every 12 hours; RECIST v 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

5. Study Design

5.1. Overall Design

Study I3Y-MC-JPCG is a Phase 2 multicenter, randomized, open-label trial in patients with HR+, HER2- mBC who have progressed on or after prior endocrine therapy and have received prior treatment with at least 2 chemotherapy regimens, of which at least 1 but no more than 2 regimens administered in the metastatic setting.

Figure JPCG.1 illustrates the study design.



Abbreviations: HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; Q12H = every 12 hours; QD = every day.
* For Arm C only. During Cycle 1, prophylactic loperamide (2 mg) will be administered orally with the first dose of abemaciclib daily. During Cycle 2 and beyond, loperamide will be administered at investigator's discretion and/or if clinically indicated.

Figure JPCG.1. Illustration of study design.

5.2. Number of Patients

Approximately 225 patients will be randomized in a 1:1:1 ratio to abemaciclib 150 mg Q12H plus tamoxifen 20 mg every day (QD) or abemaciclib 150 mg Q12H monotherapy; or abemaciclib 200 mg Q12H monotherapy plus primary prophylactic loperamide.

5.3. End of Study Definition

The primary analysis of the primary endpoint, progression-free survival (PFS), will be performed after 110 events have been observed in Arms A and C of the intent to treat (ITT) population. This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the evaluation of OS as determined by Lilly. The first OS analysis will

be at the time of PFS analysis. The final analysis of OS will occur 24 months after the last patient enters treatment. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. End of study refers to the date of the last visit or last scheduled procedure for the last patient.

5.4. Scientific Rationale for Study Design

Study JPCG is a multicenter, randomized, open-label parallel design with 3 separate treatment arms. The primary endpoint is to evaluate the efficacy of abemaciclib administered in combination with endocrine therapy compared to the efficacy of abemaciclib monotherapy in patients with pretreated HR+, HER2- mBC. The study uses standardized eligibility criteria and stratification to facilitate consistency of sample populations. The patients will be randomized 1:1:1 such that patients in each of the 3 arms will be allocated to receive investigational treatment.

5.5. Justification for Dose

In Study JPCG, abemaciclib will be administered orally at either 150 mg every 12 hours (Q12H) (Arms A and B) or at 200 mg Q12H (Arm C only) on Days 1 through 28 of a 28-day cycle.

In Study JPBA, pRb and topo II α expression in skin biopsies decreased from baseline following two weeks of twice daily dosing with both 150 and 200 mg abemaciclib, indicating inhibition of CDK 4 and CDK 6 that results in cell cycle inhibition upstream of the G1 restriction point. The plasma concentrations achieved by a dose of 150 mg Q12H in Study JPBA were similar to those associated with pRb and topo II alpha inhibition and tumor growth inhibition in the Colo-205 xenograft model (Tate et al. 2014). Study JPBA evaluated abemaciclib monotherapy at multiple dose levels in patients with advanced solid tumors. Abemaciclib was administered on a once-daily treatment schedule at 4 dose levels (50, 100, 150, and 225 mg), and steady state exposures were only marginally higher than those observed after a single dose. Therefore a twice-daily schedule at 75, 100, 150, 200, and 275 mg Q12H was evaluated.

The maximum tolerated dose (MTD) of single-agent abemaciclib was defined as 200 mg Q12H, with the dose-limiting toxicity (DLT) of Grade 3 fatigue. The most common adverse events (AEs) experienced by patients receiving abemaciclib included diarrhea and neutropenia, predominantly of low grade severity. However, the incidence and severity of these events appears to be dose-dependent. Approximately 80% of patients who received abemaciclib at 150 mg Q12H experienced treatment-emergent diarrhea, of which 16% was Grade 2 and 4% was Grade 3. Approximately 77% of patients who received abemaciclib at 200 mg Q12H experienced treatment-emergent diarrhea, of which 27% was Grade 2 and 18% was Grade 3. No Grade 4 diarrhea events were reported. No patients discontinued study treatment at either assigned dose level due to diarrhea. In Study I3Y-MC-JPBN, an ongoing Phase 2 study of single-agent abemaciclib at 200 mg Q12H, the initial onset of diarrhea was observed during the first cycle, with a median time to onset for diarrhea of approximately 7 days after initial dosing of abemaciclib. Diarrhea was managed successfully with dose omissions/reductions and antidiarrheal medication, however further reduction in the incidence and severity of treatment-emergent diarrhea may be achieved by the administration of primary prophylactic antidiarrheal

medication. Such intervention with concurrent loperamide may increase dose intensity and further optimize the clinical benefit received by patients.

Study JPBH is an ongoing Phase 1b dose escalation study of abemaciclib in combination with multiple single-agent endocrine therapy options for patients with HR+ mBC. In Study JPBH, similar safety and tolerability as single-agent abemaciclib was observed for the combination with tamoxifen (Part C, N=16). The most common adverse events (AEs) experienced by patients receiving abemaciclib plus tamoxifen included diarrhea, leukopenia and neutropenia which are predominantly of low grade severity and appear dose-dependent. Approximately, 94% of patients who received abemaciclib 200 mg Q12H plus tamoxifen 20 mg QD experienced treatment-emergent diarrhea, of which 63% were Grades 1-2 and 31% were Grade 3 (Goetz et al. 2015). There was no evidence of a PK drug interaction between abemaciclib and tamoxifen (Goetz et al. 2015). Based on the safety, tolerability, and PK results, the recommended dose for further study of abemaciclib for women with breast cancer in clinical trials is 150 mg Q12H when administered in combination with endocrine therapy. Therefore, in Study JPCG, abemaciclib will be administered orally at 150 mg Q12H in combination with tamoxifen 20 mg QD on Days 1 through 28 of a 28-day cycle.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] Have confirmed HR+, HER2-negative (HER2-) recurrent, locally advanced, unresectable, or metastatic breast cancer with evidence of relapse or disease progression on or following endocrine therapy.

- To fulfill the requirement for HR+ disease by local testing, a breast cancer must express, at least 1 of the hormone receptors (ER or progesterone receptor [PgR]). For ER and PgR assays to be considered positive, ≥1% of tumor cell nuclei must be immunoreactive by immunohistochemistry (IHC) (Hammond et al. 2010).
- To fulfill the requirement of HER2- disease by local testing on most recent biopsy, HER2- negative tumor is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH), as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (Wolff et al. 2013).

[2] Must have received prior treatment with at least 2 chemotherapy regimens:

- At least 1 of these regimens must have been administered in the metastatic setting.
- The additional chemotherapy regimens could have included, but are not limited to any of the following: capecitabine, eribulin, gemcitabine, an anthracycline, vinorelbine, or taxane.

No more than 2 prior chemotherapy regimens in the metastatic setting.

[3] Have the presence of measureable disease as defined by the Response Evaluation Criteria in Solid Tumors (for RECIST 1.1 refer to Appendix 8).

[4] Have adequate organ function for all of the following criteria, as defined below:

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥8 g/dL
	Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion.
Hepatic	
Total bilirubin	≤1.5 × ULN
ALT and AST	≤3.0 × ULN **OR** ≤5 × ULN if liver metastases are present
Renal	
Serum creatinine	≤1.5 × ULN

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal.

[5] Have a performance status ≤1 on the Eastern Cooperative Oncology Group (ECOG; Appendix 9) scale (Oken et al. 1982).

[6] Have discontinued all previous treatments for cancer and recovered from the acute effects of therapy. Patients must have discontinued from previous treatments, as shown below:

Previous Treatment	Length of Time Prior to First Dose of Study Treatment
Chemotherapy	≥21 days for myelosuppressive agents or ≥14 days for nonmyelosuppressive agents, and recovered from the acute effects of therapy (treatment-related toxicity resolved to baseline) except for residual alopecia or peripheral neuropathy.
Investigational therapy	
Immunotherapy	
Radiotherapy	
Endocrine therapy	**≥ 14 days and recovered from adverse events related to treatment.** Any number of lines of prior hormone therapy is permitted. Patients may have received prior tamoxifen in the advanced/metastatic setting. Patients receiving tamoxifen immediately preceding study entry must have demonstrated unequivocal radiological progression for eligibility.

[7] Are female and ≥18 years of age.

[8] Women of childbearing potential must have a negative serum pregnancy test at baseline (within 7 days prior to Cycle 1 Day 1), and agree to use a highly effective non-hormonal contraceptive method during the treatment period and for 3 weeks following the last dose of abemaciclib. This amount of time may be longer depending on the other treatments received during this trial.

Highly effective methods of contraception include the following:

- Intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomized partner: Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.
- Total sexual abstinence: In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

If the highly effective contraceptive methods are contraindicated or strictly declined by patients, acceptable birth control methods may be considered. These may include the combination of both of the following methods:

- Male or female condom with spermicide
- Cap, diaphragm, or sponge with spermicide

[9] Have an estimated life expectancy of ≥12 weeks.

[10] Are willing and able to make themselves available for the duration of the study and are willing and able to follow study procedures.

[11] Have given written informed consent prior to any study-specific procedures.

Refer to Appendix 2 for study governance, regulatory, and ethical considerations.

[12] Are able to swallow oral medications.

6.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[13] Have a personal history of any of the following conditions: syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Subjects with controlled atrial fibrillation for >30 days prior to study treatment are eligible.

[14] Have history or evidence of central nervous system (CNS) metastasis on the MRI of brain obtained at baseline.

[15] Have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix or breast), unless in complete remission with no therapy for a minimum of 3 years.

[16] Are pregnant or lactating.

[17] Have active bacterial or fungal infection (that is, requiring IV [intravenous] antibiotics at the time of initiating study treatment) and/or detectable viral infection (for example, human immunodeficiency virus [HIV] positivity or known active or inactive hepatitis carrier [for example, hepatitis B surface antigen [HBSAg], or hepatitis C antibodies [HCAb]). Screening is not required for enrollment.

[18] Have received prior treatment with any CDK4 and CDK6 inhibitor.

[19] Known hypersensitivity to loperamide hydrochloride or tamoxifen or to any of the excipients of either product.

[20] Have a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea.

[21] Have visceral crisis. Visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease.

[22] Are currently enrolled in a clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[23] History or evidence of thromboembolic disease including any of the following, history of stroke, deep vein thrombosis (DVT), or pulmonary embolism (PE). Patients with documented hypercoagulable state are not eligible.

[24] Are receiving treatment with Warfarin or coumarins.

6.3. Lifestyle Restrictions

Patients should refrain from drinking grapefruit juice while on study drug.

Patients should not donate blood while on study drug and for 3 months after discontinuing study treatment.

Patients must agree to use a highly effective non-hormonal contraceptive method while on study drug and for 3 months after discontinuing study treatment (see Section 6.2).

6.4. Screen Failures

Re-screening of individuals who do not meet the criteria for participation in this study is not permitted.

Repeating of laboratory tests during the 14-day screening period does not constitute re-screening.

7. Treatments

7.1. Treatments Administered

Patients will be randomized to one of the following treatment arms.

Table JPCG.6 shows the treatment regimens.

Table JPCG.6. Treatment Regimens

Arm	Abemaciclib Dose	Tamoxifen Dose	Treatment Schedule	Route of Administration
A	150 mg Q12H	20 mg QD	D1 to D28 of a 28-day cycle	Orally
B	150 mg Q12H	NA	D1 to D28 of a 28-day cycle	Orally
C[a]	200 mg Q12H	NA	D1 to D28 of a 28-day cycle	Orally

Abbreviations: Q = every; Q12H = every 12 hours; QD = every 24 hours.

[a] Arm C patients only. Prophylactic loperamide 2 mg orally is administered with the first dose of abemaciclib daily.

Abemaciclib will be administered orally at the assigned dose level Q12H (± approximately 2 hours) in each treatment arm, respectively. Abemaciclib capsules should be taken whole and not opened, crushed, chewed, dissolved in water, or altered in any way and may be taken with or without food. If a patient misses a dose, the dose should be omitted. If a patient vomits after taking a dose, the dose should not be retaken. Patients will receive either 150 mg of abemaciclib orally Q12H in combination tamoxifen (Arm A), 150 mg Q12H of abemaciclib monotherapy (Arm B), or abemaciclib 200 mg Q12H plus primary prophylactic loperamide (Arm C).

For Arm A, during Cycles 1 through 3, when abemaciclib is scheduled to be administered on the same day as tamoxifen and PK samples are drawn, abemaciclib should be given at the same time as tamoxifen.

For Arm C, during Cycle 1, prophylactic loperamide, 2 mg orally, will be administered with the first dose of abemaciclib daily. If the daily dose of loperamide is forgotten with the first dose of abemaciclib, it should be taken with the second dose of abemaciclib that day or after the first loose stool. Patients may take an additional 2 mg (1 capsule/tablet) dose of loperamide after each loose stool up to a maximum of 16 mg (8 capsules/tablets) per day (including doses taken with abemaciclib). In the event a patient experiences Grade 2 diarrhea (4 to 6 loose stools per day above baseline) despite loperamide prophylaxis, a dose reduction (-1 level) of abemaciclib should be considered before additional doses of loperamide are taken. If diarrhea recurs within 24 hours despite a dose reduction, additional doses (2 mg each) of loperamide may be taken at the investigator's discretion. Loperamide may be discontinued 28 days after initiation of abemaciclib therapy at the investigator's discretion. Loperamide dose should be omitted if the abemaciclib dose is omitted for a reason other than diarrhea. Loperamide administration, including dose adjustments (increases and/or decreases) and changes for indicated use, will be captured on the electronic case report form (eCRF). Additional loperamide dose modifications are described in Section 7.4.1.1.1.3.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient/study site personnel/legal representative
- verifying that instructions are followed properly
- maintaining accurate records of study treatment dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless Lilly and the site have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labelling

Study treatment will be provided as outlined in Section 7.5. Clinical trial materials will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomly assigned to either Arm A, Arm B, or Arm C.

Approximately 225 patients will be randomized in a 1:1:1 ratio. Randomization will be stratified by the presence of liver metastases (yes versus no) and prior tamoxifen therapy in the advanced/metastatic setting (yes versus no).

The interactive web-response system (IWRS) will use randomization factors to assign study treatment to each patient.

7.2.1. Selection and Timing of Doses

Abemaciclib will be administered orally at 150 mg (Arms A and B) or 200 mg (Arm C) Q12H on Days 1 through 28 of a 28-day cycle (± 3 days). Details on treatment administration are described in Section 7.1.

Patients will continue to receive study treatment until evidence of disease progression or any discontinuation criteria are met (see Section 8).

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

7.4.1. Special Treatment Considerations

7.4.1.1. Dose Adjustments and Delays

Table JPCG.7. Toxicity Dose Adjustments and Delays of Abemaciclib

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity Section 7.4.1.1.2.1	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Hematologic Toxicity Section 7.4.1.1.2.1	Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity Section 7.4.1.1.2.1	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic toxicity: If patient requires administration of blood cell growth factors. Sections 7.4.1.1.2.1 and 7.7.2	Regardless of severity. (Use of growth factors according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2	Dose **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that led to the use of growth factor
Nonhematologic Toxicity[b] (except diarrhea and ALT increased) Section 7.4.1.1.2.1	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Nonhematologic Toxicity Section 7.4.1.1.2.1	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 7.7.1.1	Grade 2 that does not resolve within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose reduction is NOT required.
Diarrhea Section 7.7.1.1	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures or any Grade of diarrhea that requires hospitalization	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 7.7.1.1	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT Increased Section 9.4.2.1	Persistent or recurrent[a] Grade 2 (>3.0-5.0×ULN), or Grade 3 (>5,0-20.0×ULN)[c]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT Increased Section 9.4.2.1	Grade 4 (>20.0×ULN)	Abemaciclib therapy **MUST** be discontinued.	Abemaciclib therapy **MUST** be discontinued.
ALT Increased with increased total bilirubin, in the absence of cholestasis	Grade 3 increased ALT (>5.0 x ULN) with total bilirubin >2 x ULN	Abemaciclib therapy MUST be discontinued	Abemaciclib therapy MUST be discontinued

Abbreviation: ALT = alanine transaminase; ASCO = American Society of Clinical Oncology.
Note: MUST = mandatory.

a Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).This does not include events in the same class (for example, neutropenia followed by anemia 1 month later). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose if the patient satisfies the following conditions:
- shows stable hematological counts (≤Grade 2) during that timeframe
- has absence of any infectious sign or risk factor
- is getting benefit from study treatment

b Additional guidance for renal and hepatic monitoring is in Section 9.4.2.

c Grade 3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 9.4.2.1 for additional guidance for hepatic monitoring.

Any questions regarding the dose reduction decision should be discussed with the Lilly clinical research physician (CRP).

7.4.1.1.1. Dose Adjustments

7.4.1.1.1.1. Abemaciclib

Dose adjustments as outlined in Table JPCG.8 are allowed both within a cycle and between cycles. Abemaciclib must be reduced sequentially by one dose level.

For patients requiring dose reduction(s), any re-escalation to a prior dose level is permitted only after consultation with the Lilly clinical research physician (CRP). After re-escalation, subsequent dose adjustments should be based on the dose of abemaciclib that the patient is currently receiving.

Table JPCG.8. Dose Adjustments of Abemaciclib

Arm	Dose Adjustment	Oral Dose	Frequency
A and B	0	150 mg	Q12H
	1	100 mg	Q12H
	2	50 mg	Q12H
C	0	200 mg	Q12H
	1	150 mg	Q12H
	2	100 mg	Q12H

Abbreviation: Q12H = every 12 hours.

For Arms A and B, if a patient receiving the 50 mg Q12H dose of abemaciclib requires further dose reduction, the patient should be discontinued from study treatment. For Arm C, if a patient receiving the 100 mg Q12H dose of abemaciclib requires a further dose reduction, the patient should be discontinued from study treatment. Based on the judgment of the investigator, if a patient is receiving clinical benefit from study therapy and requires further dose reduction than

what is outlined in Table JPCG.8, the investigator must discuss with Lilly CRP prior to further dose reduction.

For Arm A, in the event that abemaciclib must be discontinued due to tolerability, a patient may continue to receive tamoxifen at the investigator's discretion.

7.4.1.1.1.2. Tamoxifen (Arm A only)

Dose adjustments for tamoxifen are not planned. If a dose of tamoxifen is forgotten, tamoxifen dosing will be continued the following day without change (meaning missed doses will not be made up). See Section 7.4.1.1.2.2 for details on dose delays for tamoxifen.

In the event there is evidence of metrorrhagia, rapid gynecological examination should be performed according to local institutional standards. Tamoxifen will be permanently discontinued in the event of a thromboembolic episode or atypical hyperplasia of the endometrium.

If tamoxifen is permanently discontinued due to tolerability, a patient may continue to receive abemaciclib at the investigator's discretion.

7.4.1.1.1.3. Loperamide

Loperamide will be dispensed via IWRS for all patients in all the arms; however, only patients in Arm C should take loperamide prophylactically. Patients in Arms A and B should only take loperamide once the patient experiences diarrhea and requires treatment.

For Arm C, during Cycle 1, prophylactic loperamide should be taken with the first dose of abemaciclib. Loperamide may be discontinued 28 days after the initiation of abemaciclib therapy at the investigator's discretion. However, if the patient develops diarrhea after loperamide discontinuation, loperamide administration should be reinitiated at the investigator's discretion. If abemaciclib dosing is suspended for a reason other than diarrhea, loperamide administration should also be suspended and reinitiated when abemaciclib dosing is reinitiated.

If a patient experiences constipation or other symptoms related to loperamide dosing (for example, abdominal cramping), the investigator may reduce/stop the patient's dosing of loperamide. If a patient does not have a bowel movement for ≥36 hours, loperamide is to be suspended until bowel movements resume. If loperamide administration resumes, the dose may be adjusted (e.g. once every other day) at the investigator's discretion. Investigators should take into account patient's history and/or risk of constipation when considering increases in loperamide dosing, more than prophylactic doses taken with abemaciclib.

7.4.1.1.2. Dose Delays and Omission

7.4.1.1.2.1. Abemaciclib

Table JPCG.9 provides general guidelines for dose delays of abemaciclib.

Table JPCG.9. General Dose Delays of Abemaciclib

General Dose Delays	Time Permitted for Delay
Delay of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances	7 days
Toxicity-time for recovery to baseline or at least Grade 1 for nonhematologic and at least Grade 2 for hematologic toxicity	Up to 14 days

Both dose suspension (within a cycle) and cycle delay are permitted. When a dose suspension or cycle delay occurs related to toxicity (defined as an AE possibly related to study treatment per investigator judgment), abemaciclib and/or tamoxifen (Arm A only) may be suspended or delayed as determined by the investigator's judgment, but only for a maximum of 14 days.

Study treatment may be held up to 14 days within a cycle or at start of next cycle to permit sufficient time for recovery from the toxicity. If a dose suspension occurs within a cycle, the investigator may resume study drug dosing at the same dose level for the remainder of the cycle or, for abemaciclib only, at a reduced dose (assuming resolution to at least Grade 1 for nonhematological and at least Grade 2 for hematological toxicity). If the patient experiences the same toxicity with the same or greater severity (Common Terminology Criteria for Adverse Events [CTCAE] grade) requiring a dose suspension within a cycle or at start of the next cycle, the patient must be dose reduced for abemaciclib and not re-challenged a second time at the prior dose level (see Table JPCG.7).

Patients not recovering from toxicity within 14 days should be considered for discontinuation of study treatment. In exceptional circumstances, a delay >14 days is permitted upon agreement between the investigator and the Lilly CRP and abemaciclib dose adjustment is to be considered.

A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation. In exceptional cases of planned delays (including but not limited to vacation or holidays), additional study treatment may be dispensed.

In the event of a cycle delay due to logistical reasons (for example, due to patient availability), the patient should continue on study treatment if the patient has adequate drug supply. If a patient's treatment is interrupted as a result of not having sufficient drug supply, the cycle may be delayed up to 7 days (and not be considered a protocol violation). In exceptional circumstances, a delay >7 days is permitted upon agreement between the investigator and the Lilly CRP.

7.4.1.1.2.2. Tamoxifen (Arm A only)

In the event of the occurrence of Grade 3-4 toxicity related to tamoxifen, tamoxifen dosing should be stopped for a maximum of 14 days. If the toxicity improves during this period, tamoxifen may be resumed, if possible. If the toxicity does not improve within 14 days or recurs upon resumption, tamoxifen should be permanently discontinued. If tamoxifen is permanently

discontinued due to tolerability, the patient may continue to receive abemaciclib at the investigator's discretion.

7.5. Preparation/Handling/Storage/Accountability

Abemaciclib, tamoxifen, and loperamide will be supplied by Lilly and labeled according to country regulatory requirements. All capsules/tablets should be stored according to their associated product label and taken as indicated. Patients should store these agents in the original package provided and according to the product label (where applicable) and be instructed to keep all medications out of reach of children.

7.6. Treatment Compliance

Patient compliance with abemaciclib will be assessed by reconciliation at qualified visits (e.g. Day 1 of each Cycle). Study medication administration data will be recorded in the patient's medical record and eCRF.

Patients who are significantly noncompliant will be discontinued from the study. A patient will be considered significantly noncompliant if she misses more than 25% cumulative days of abemaciclib (full doses) during the study. Similarly, a patient will be considered significantly noncompliant if she is judged by the investigator to have intentionally or repeatedly taken more than (>125%) the prescribed amount of medication. Abemaciclib dose suspensions or delays related to toxicity may occur and will not result in a patient being considered as noncompliant.

Patients randomized to Arm A, will be assessed by authorized study personnel for noncompliance of tamoxifen. All tamoxifen administration data will be recorded in the patient's medical record and eCRF.

Patients randomized to Arm C will be assessed by authorized study personnel for noncompliance of prophylactic loperamide only during Cycle 1. Prophylaxis during Cycle 2 and beyond is at the discretion of the investigator. All loperamide administration, including but not limited to dose adjustments during Cycle 1, will be recorded in the patient's medical record and eCRF.

7.7. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, concomitant medications, and supplements must be captured at each visit in the eCRF. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term follow-up visit.

With the exceptions listed in the sections below, no other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy (with the exception of patients randomized to Arm A and receiving combination therapy with tamoxifen), radiation, surgery for cancer, or experimental medications will be permitted while patients are on study treatment. Megestrol acetate as an appetite stimulant is not permitted.

Patients may remain on concomitant therapy with approved bisphosphonates or approved RANK ligand targeted agents (for example, denosumab). Patients who remain on bone modifying

agents are permitted to switch after randomization as long as it is in the absence of disease progression, and due to reasons, including but not limited to tolerability. The investigator must discuss with Lilly CRP prior to the change. Patients not currently receiving therapy with bone modifying agents are not permitted to start bisphosphonates or RANK ligand targeted agents after randomization.

Abemaciclib is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies, coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (AUC) to abemaciclib by 3.4 fold (Study I3Y-MC-JPBE) and coadministration of rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study I3Y-MC-JPBF). Therefore, grapefruit juice as well as inducers and strong inhibitors of CYP3A should be substituted or avoided if possible (Appendix 6).

The results from in vitro studies in cultured human hepatocytes indicate that abemaciclib and its major metabolites, LSN2839567 and LSN3106726, down regulate mRNA of CYPs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A, at clinically relevant concentrations. The mechanism of mRNA down regulation and its clinical relevance are not yet understood. Therefore, care should be taken when coadministering substrate drugs of the above CYPs with narrow therapeutic margin (Appendix 6).

Reduced efficacy of tamoxifen has been reported with concomitant usage of some selective serotonin reuptake inhibitor antidepressants (for example, paroxetine) in some studies, and pharmacokinetic interactions of tamoxifen with CYP2D6 inhibitors have also been reported (Stearns et al. 2003; tamoxifen product information). As a reduced effect of tamoxifen cannot be excluded, coadministration with potent CYP2D6 inhibitors (for example, paroxetine, fluoxetine, quinidine, cinacalcet, or bupropion) should, whenever possible, be avoided.

7.7.1. Supportive Care

Patients should receive full supportive care to maximize quality of life. Patients will receive supportive care based on the judgment of the treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP. Use of any supportive care therapy should be reported on the eCRF.

Guidelines regarding the use of other specific supportive care agents are presented below.

7.7.1.1. Supportive Management for Diarrhea

At enrollment, patients should receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy, if not already receiving such therapy (for example, loperamide), and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.

- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to either baseline or Grade 1, study drug should be suspended until diarrhea is resolved to baseline or Grade 1.
- When study drug recommences, dosing should be adjusted as outlined in Table JPCG.7 and Section 7.4.1.1.1.1.

In cases of significant diarrhea, Grade 2 through 4 (Appendix 7), which has not responded to interventions as outlined above, if the investigators are considering the addition of steroids to treat potential colitis, the sponsor strongly recommends an endoscopic procedure to document colitis prior to initiating steroids.

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement.

7.7.2. Growth Factor Therapy

Growth factors should not be administered to a patient to satisfy study inclusion criteria.

Growth factors may be administered in accordance with ASCO guidelines (Smith et al. 2015). Dosing of abemaciclib must be suspended if the administration of growth factors is required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of abemaciclib must be reduced by 1 dose level on recommencement, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

7.8. Treatment after the End of the Study

Study completion will occur following the final analysis of overall survival, as determined by Lilly. Investigators will continue to follow the Schedule of Activities (refer to Section 2) for all patients until notified by Lilly that study completion has occurred.

7.8.1. Continued Access

Patients who are still on study treatment at the time of study completion may continue to receive study treatment if they are experiencing clinical benefit and no undue risks (Figure JPCG.2).

Continued access period will apply to this study only if at least 1 patient is still on abemaciclib when study completion occurs. Lilly will notify investigators when the continued access period begins.

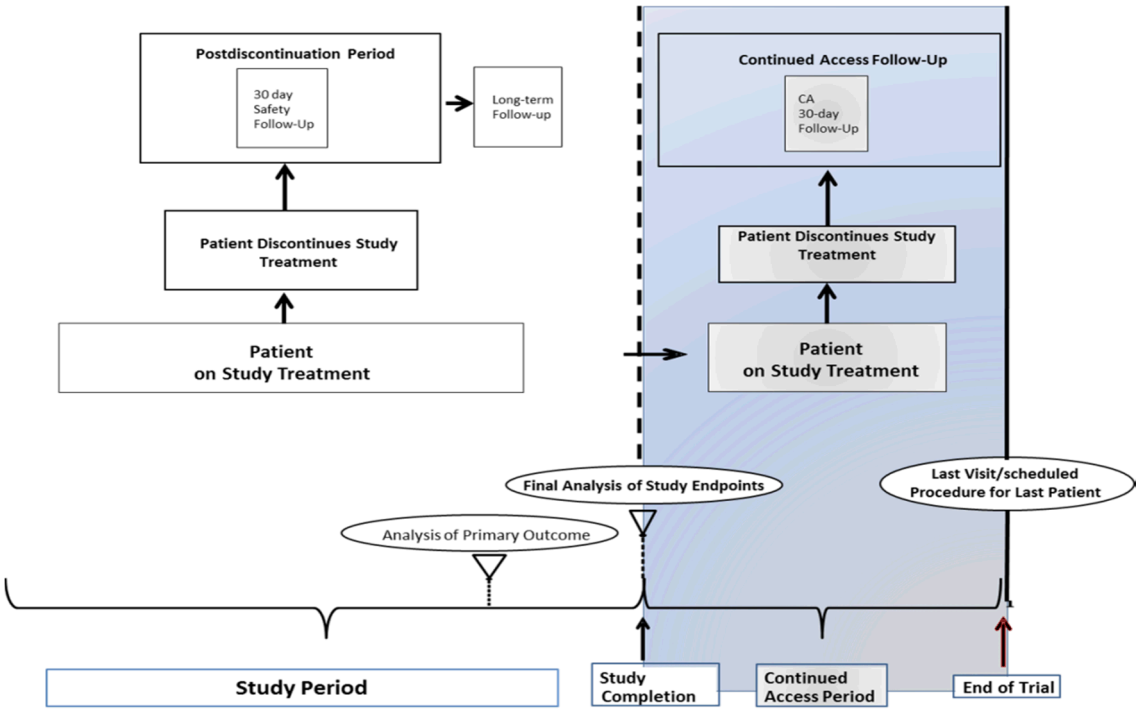
Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

During the continued access period, all AEs, SAEs, and abemaciclib exposure will be reported on the eCRF at least every 28 days when drug is returned and dispensed. SAEs should be reported immediately and patients should not wait for a drug return/dispensing visit. SAEs will also be reported to Lilly Global Patient Safety. In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications and hospitalizations) in order to evaluate the reported SAE.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

Follow-up procedures will be performed as shown in the Continued Access Schedule of Activities (Table JPCG.4).



Abbreviation: CA = continued access.

Figure JPCG.2. Continued access diagram.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Patients will be discontinued from study treatment in the following circumstances:

- the patient is enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- investigator decision
  - the investigator decides that the patient should be discontinued from the study or study drug
  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug occurs prior to introduction of the new agent
- patient decision
  - the patient requests to be withdrawn from the study or study drug
  - the patient's designee (for example, parents, legal guardian, or caregiver) requests that the patient be discontinued from study treatment
- sponsor decision
  - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- the patient becomes pregnant during the study. See Section 9.2 regarding regulatory reporting requirements on fetal outcome and breastfeeding.
- the patient is significantly noncompliant with study procedures and/or treatment
- disease progression
- unacceptable toxicity

Patients who are discontinued from study treatment will have follow-up procedures performed as shown in the Schedule of Activities (Table JPCG.3).

For patients who discontinue study treatment without objectively measured progressive disease, continue to evaluate tumor response according to planned tumor assessment schedule by the same method used at baseline and throughout the follow-up periods until patient has objective disease progression or until the study's primary analysis of PFS. After the patient has objective disease progression, radiologic tests are no longer required.

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study treatment.

8.2. Discontinuation from the Study

Patients will be discontinued from the study in the following circumstances:

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- the patient becomes pregnant during the study. See Section 9.2 regarding regulatory reporting requirements on fetal outcome and breastfeeding.
- the investigator decides that the patient should be discontinued from the study
- the patient requests to be discontinued from the study
- the patient's designee (for example, parents, legal guardian, or caregiver) requests that the patient be discontinued from the study.

Patients who discontinue from the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Table JPCG.3).

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

Study site personnel, or an independent third party, will attempt to collect the survival status for all randomized patients who are lost to follow-up, including randomized patients who do not receive study treatment, within legal and ethical boundaries. Public sources may be searched for survival status information. If the patient's survival status is determined, the survival status will be documented, and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect survival status information.

9. Study Assessments and Procedures

Section 2 (Table JPCG.1, Table JPCG.2, and Table JPCG.3) provides the Schedule of Activities for this study.

Appendix 3 provides a list of the laboratory tests that will be performed for this study.

Appendix 4 provides the schedule for collection of samples in this study.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Efficacy Assessments at Baseline and during Study Treatment

Tumor assessments will be performed at baseline (within 28 days from first dose of study therapy) and every 8 weeks (- 7 days) by investigator. The same method of assessment and technique used at baseline should be used for each subsequent assessment thereafter. Radiological scan of the chest, abdomen, and pelvis is required. See Section 10.3.1 for definitions of the efficacy endpoints. All tumor assessment images must be submitted for potential central review.

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, magnetic resonance imaging (MRI) is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Intravenous and oral contrast is required unless medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST v.1.1 (Eisenhauer et al. 2009).

For only those patients with bone lesions identified by bone scintigraphy at baseline, directed imaging using one of the following methods will be performed at baseline: X-ray, CT scan with bone windows, or MRI. Directed imaging using the same method as at the baseline bone lesion assessment should be repeated every 8 weeks (-7 business days), and within 14 days of clinical progression.

For patients with visible tumors (such as skin lesions), photography will be performed at baseline and every 8 weeks (-7 business days), and within 14 days of clinical progression. Each photographic image of the tumor should include a ruler. Photographic images may be taken

more frequently based upon the discretion of the investigator or following the identification of new skin lesions postbaseline.

For patients continuing treatment during the Continued Access Period (after study completion), efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator.

9.1.2. Efficacy Assessments during Postdiscontinuation Follow-up

Tumor assessments will be performed within 14 days of clinical progression and during postdiscontinuation follow-up as described in the Schedule of Activities (see Section 2).

For those patients who discontinue study treatment without objectively measured PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response via radiological imaging and measurement of visible tumors (if applicable) approximately every 8 weeks from the first dose of study therapy by the same method used at baseline and throughout the study until the patient has objective disease progression or until primary analysis of PFS. In addition, anticancer therapies initiated after study treatment discontinuation will be collected during this follow-up period. After the patient has objective disease progression, radiologic tests and tumor assessments are no longer required and the patient will continue with postdiscontinuation follow-up approximately every 90 days until the patient's death or overall study completion. For patients with nonmeasurable bone lesions identified at baseline, bone scans are to be performed approximately every 24 weeks until objective disease progression or primary PFS analysis.

Lilly will continue to collect survival data on all patients but may reduce data collection for other efficacy data. Lilly will notify investigators when this reduced data collection can begin (see Section 7.8.1).

9.1.3. Appropriateness of Assessments

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional oncology trials.

9.2. Adverse Events

The investigator will use Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (NCI 2009) to assign AE terms and severity grades.

Investigators are responsible for:

- monitoring the safety of patients in this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient
- the appropriate medical care of patients during the study
- documenting their review of each laboratory safety report
- following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused

the patient to discontinue study treatment before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the informed consent form (ICF) is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, study site personnel will record via eCRF any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study procedure or study treatment via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatments, or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the study treatment and/or study procedure and the AE.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must report any dose modifications or treatment discontinuations that result from AEs to Lilly or its designee via eCRF, clarifying, if possible, the circumstances leading to the dose modification or discontinuation of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per International Conference on Harmonisation (ICH) definition, are reportable in the same timeframe as SAEs to meet certain local requirements.

Therefore, these events are considered serious for collection purposes:

- is a new cancer (that is not a condition of the study);
- is associated with an overdose.

Although all AEs after signing the ICF are recorded in the eCRF, SAE reporting begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE but should be reported. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Planned hospitalizations or procedures for preexisting conditions that were recorded in the patient's medical history at the time of enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

9.2.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the IB and/or Product Label (abemaciclib and/or tamoxifen [Arm A only]).

9.4. Safety

9.4.1. Other Safety Measures

For each patient, electrocardiograms (ECGs), vital signs, laboratory tests, or other tests should be collected as shown in the Schedule of Activities (Section 2).

Blood samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Enrollment and treatment decisions may be based upon results performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol deviations.

Investigators must document their review of each laboratory safety report.

Any clinically significant findings that result in a diagnosis and that occur after the patient signs the informed consent form (ICF) should be reported to Lilly or its designee as an AE via eCRF.

9.4.2. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.4.2.1. Special Hepatic Safety Data Collection

If a study patient experiences elevated alanine aminotransferase (ALT) ≥5-fold the upper limit of normal (ULN) and elevated total bilirubin (TBL) ≥2-fold ULN, or ALT >8x ULN for patients with underlying baseline hepatic metastases, liver tests (Appendix 5), including ALT, AST, TBL, direct bilirubin, gamma glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (Appendix 5) and in consultation with the Lilly CRP. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels. Additional diagnostic testing should be considered to rule out cause of increased liver enzymes per the investigator's discretion.

Hepatic monitoring tests (Appendix 5) should be collected in the event that 1 or more of the following conditions is met for the patient during the course of the study:

- ALT ≥5×ULN and TBL ≥2×ULN
- ALT>8x ULN for patients with underlying hepatic metastasis
- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests.

9.4.2.2. Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C calculated glomerular filtration rate. Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function. See Appendix 3.

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities (Table JPCG.7).

9.4.2.3. Venous Thromboembolic Events

In the randomized Phase 3 studies in breast cancer patients who received abemaciclib in combination with endocrine therapy, there was a greater number of patients who experienced venous thromboembolic events (VTEs) in the abemaciclib plus endocrine therapy arm than in the placebo plus endocrine therapy arm. The majority of the events were non-serious and were treated with low-molecular-weight heparin. Generally, these events did not result in discontinuation of the study treatment. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. For suspected or confirmed VTE (eg. deep vein thrombosis or pulmonary embolism), treatment should occur according to usual clinical practice.

9.5. Pharmacokinetics

Pharmacokinetic (PK) samples will be collected as shown in Appendix 4.

Blood samples will be used to determine the concentrations of abemaciclib and its metabolites in addition to tamoxifen and its active metabolite endoxifen.

Bioanalytical samples collected to measure abemaciclib and its metabolites or tamoxifen and its metabolite endoxifen concentrations will be retained for a maximum of 1 year following the last patient visit for the study.

9.6. Pharmacodynamics

See Section 9.8.

Samples collected will be identified by the patient number (coded) and retained at a facility selected by Lilly for a maximum of 15 years following the last patient visit for the study.

9.7. Pharmacogenomics

9.7.1. Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in Appendix 4, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in cancer. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/institutional review boards (IRBs) impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of abemaciclib or after abemaciclib becomes commercially available.

Molecular technologies are expected to improve during the 15 year storage period and therefore cannot be specifically named. However, existing technologies include whole genome and exome sequencing, genome-wide association studies, multiplex assays, candidate gene studies, and epigenetic analyses. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics (PD), mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

As part of Lilly's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to abemaciclib, cell cycle, immune response/functioning, and /or cancer, and/or for related research methods or validation of diagnostic tools or assays.

Samples for biomarker research will be collected as specified in Appendix 4, where local regulations allow. It is possible that biomarker data for patients in the study has already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 9.8.1 and 9.8.2.

9.8.1. Samples for Nonpharmacogenetic Biomarker Research

Plasma samples for nonpharmacogenetic biomarker research will be collected as specified in Appendix 4 where local regulations allow.

Samples will be examined for biomarkers related to cancer, variable response to abemaciclib or study treatment, the mechanism of action of abemaciclib, immune response/functioning, and/or for research-related methods, or validating diagnostic tools or assays.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of abemaciclib or after abemaciclib becomes commercially available.

9.8.2. Tissue Samples for Research

Tumor tissue will be examined for biomarkers related to cancer, abemaciclib, immune response/functioning, and/or cell cycle.

Collection of the following tumor tissue sample is **required** for all patients in order to participate in this study:

- an archived tumor sample, if available and not restricted by local regulations

The absence of available archived tumor specimen does not preclude a patient from study entry.

Formalin-fixed paraffin-embedded tumor tissue obtained from the primary tumor or metastatic site should be provided as a block or unstained slides. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided. Pathology report accompanying archival tissue may also be requested. The report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Archival blocks will be sectioned and returned to the study site, at the end of the study. Slides and tissue samples collected on-study will not be returned.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of abemaciclib or after abemaciclib becomes commercially available.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies, including mutation profiling, copy number variability, gene expression, multiplex assays, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations with these biomarkers and clinical outcomes.

9.9. Health Outcomes/Quality of Life

Self-reported questionnaires will be administered as shown in the Schedule of Activities (Section 2) in countries where the questionnaires have been translated into the native language of the region and are linguistically validated.

The primary health outcomes research goal is to determine if abemaciclib therapy is able to palliate pain, as measured by the modified Brief Pain Inventory-Short Form (mBPI-sf). Additionally, the EORTC Quality of Life Questionnaire Core-30 version 3 (EORTC QLQ-C30) will assess the broader impact of abemaciclib therapy on quality of life.

Patient-reported questionnaires should be completed by patients when a language translation is available in which the patient is fluent or literate.

At each time point identified in the Schedule of Events (Section 2), a paper copy of each questionnaire should be administered to the patient prior to extensive interaction with site staff. The mBPI-sf should be collected first, followed by the EORTC QLQ-C30.

9.9.1. Pain Assessment

The mBPI-sf (Cleeland and Ryan 1994) is an 11-item instrument used as a multiple-item measure of cancer pain intensity. In addition to pain intensity (4 items), the mBPI-sf is designed for patients to record the presence of pain in general, pain relief, and pain interference with function (general activity, mood, ability to walk, ability to perform normal work, relations with others, sleep, enjoyment of life).

Responses for the mBPI-sf items are captured through the use of 11-point numeric rating scales anchored at 0 (*no pain* or *does not interfere*) and 10 (*pain as bad as you can imagine* or *completely interferes*). The mBPI-sf recall period is 24 hours and typical completion time for this instrument is less than 5 minutes.

Use of pain medication will be assessed in conjunction with the mBPI-sf assessment. Data on each individual prescription and over-the-counter analgesic at the baseline visit will be recorded on the Concomitant Medication page. The use of pain medications should be reviewed with the patient at each subsequent visit. Any changes to analgesic use (new or stopped analgesics) compared to the preceding cycle should be recorded on Concomitant Medication page.

9.9.2. Health-Related Quality of Life

Broadly used in cancer trials, validated, and available in over 80 different languages, the EORTC QLQ-C30 is a reliable and validated tool. The EORTC QLQ-C30 self-reported general cancer instrument (Aaronson et al. 1993) consists of 30 items covered by 1 of 3 dimensions:

- global health status/quality of life (2 items)
- functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning)
- symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)

The EORTC QLQ-C30 questionnaire is administered per the Schedule of Events (Section 2). The recall period is the past week and completion time is typically 5 to 7 minutes.

9.9.3. Resource Utilization

Utilization data overall and by arm will be summarized descriptively by category (for example, transfusions, antidiarrheals, and hospitalization days) as appropriate.

10. Statistical Considerations

10.1. Sample Size Determination

The primary objective of PFS will be tested at an experiment-wise one-sided alpha level of .10. Assuming a hazard ratio (HR) of .667 for Arm A compared to Arm C (corresponding to an increase in mPFS from approximately 6 months to 9 months), approximately 110 events across the two arms are required to achieve approximately 80% power. Assuming 30% censoring, 75 patients per arm will be enrolled (225 patients total).

The informal non-inferiority rule for comparing Arm B to Arm C is as follows: if the observed PFS hazard ratio is less than 1.2, Arm B will be considered non-inferior to Arm C. Assuming 110 events across the 2 arms, this design provides 80% probability to show the PFS HR is less than 1.2, assuming a true HR = 1.

The study will enroll approximately 225 patients in a 1:1:1 randomization (approximately 75 patients per treatment arm for women with previously treated HR+, HER2- mBC).

10.2. Populations for Analyses

The following populations will be defined for this study:

Intention-to-Treat (ITT) population: will include all randomized patients. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized and not by actual treatment received. This population will be used for all baseline, efficacy, and health economics analyses.

Safety population: will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose of study treatment a patient actually received, regardless of the arm to which she was randomized. The safety population will be used for all dosing/exposure, safety, and resource utilization analyses.

Pharmacokinetic population: will include all randomized patients who received at least 1 dose of study treatment and have at least 1 postbaseline evaluable PK sample.

Biomarker population: will include all randomized patients with evaluable baseline blood, plasma, or tissue samples. Patients with postbaseline samples will be a subset of this defined biomarker population.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Unless otherwise stated, all tests of treatment effects will be conducted at a 1-sided alpha level of .025, and all confidence intervals (CIs) will be given at a 2-sided 95% level. The primary objective of PFS and secondary objective of OS will be tested at an experiment-wise one-sided alpha level of .10.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Efficacy Analyses

10.3.1.1. Progression Free Survival

The primary endpoint of this study is PFS. PFS time is measured from the date of randomization to the date of investigator-determined objective progression as defined by RECIST v1.1, or death from any cause. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment (if available) or date of randomization if no post initiation (that is, postbaseline) radiographic assessment is available. The detailed censoring rules are described in Table JPCG.10.

Table JPCG.10. PFS Event/Censoring Scheme

Situation[a]	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)[b]
Unless		
No baseline radiological tumor assessment available	Censored	Date of randomization
No adequate postbaseline radiological tumor assessment available and death reported after 2 scan intervals following randomization[b,c]	Censored	Date of randomization
New anticancer treatment started and no tumor progression or death within 14 days	Censored	Date of adequate radiological assessment prior to (start of new therapy +14 days) or date of randomization (whichever is later)
Tumor progression or death documented after 2 or more scan intervals following last adequate radiological tumor assessment or randomization (whichever is later)[b,c]	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)[b]

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

a Symptomatic deterioration (that is, symptomatic progression that is not radiologically confirmed) will not be considered as tumor progression.

b Adequate radiological tumor assessment refers to an assessment with one of the following responses: CR, PR, SD, or PD.

c Refer to the statistical analysis plan for the definition of 2 scan intervals, including any adjustment for scan window.

There is one planned primary analysis for PFS in this study, which will be performed after 110 events have been observed in Arms A and C of the ITT population based on investigator

assessment. The PFS analysis to test the superiority of abemaciclib plus tamoxifen (Arm A) to abemaciclib plus prophylactic loperamide (Arm C) in improving PFS time will be performed on the ITT population at an experiment-wise one-sided alpha level of .10 and will use the log-rank test stratified by the randomization factors of presence of liver metastases and prior use of tamoxifen in the advanced/metastatic setting. The corresponding hazard ratio (HR) between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata. An additional unstratified Cox regression model will be employed to explore the effects of the stratification variables on treatment response. In addition, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the PFS curves as well as PFS rates at 3, 6, 9, and 12 months for each treatment group. These rates will be compared based on a normal approximation for the difference between the rates.

Arm B (abemaciclib 150 mg) will be compared against Arm C (abemaciclib 200 mg + prophylactic loperamide) in an informal manner. If the PFS HR is less than 1.2, Arm B will be considered non-inferior to Arm C ("informal Phase 2 non-inferiority"). This comparison will use the same methodology described above. Arm A will not be compared against Arm B using a log-rank test or Cox HR model, but the Kaplan-Meier estimates for Arms A and B will be available from the previous analyses.

10.3.1.2. Objective Response Rate, DCR, CBR, and DoR

Other secondary efficacy endpoints will be defined as shown in Table JPCG.11.

Table JPCG.11. Other Secondary Efficacy Endpoints

Endpoint	Definition
ORR	The proportion of patients with CR or PR according to RECIST v1.1
DCR	The proportion of patients with CR, PR, or SD according to RECIST v1.1
CBR	The proportion of patients with CR, PR, or SD ≥6 months according to RECIST v1.1
DoR	The time from the date of first evidence of a CR or PR to the date of objective progression or death from any cause, whichever is earlier

Abbreviations: CBR = clinical benefit rate; CR = complete response; DCR = disease control rate; DoR = duration of response; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST v 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SD = stable disease.

The objective response rate (ORR), disease control rate (DCR), and clinical benefit rate (CBR) of each treatment arm will be calculated using the ITT population. All rates will be compared between the 3 treatment arms based on a normal approximation for the difference between the rates.

The duration of response (DoR) time is defined only for responders (patients with a best response of complete response [CR] or partial response [PR]). A Kaplan-Meier analysis of DoR will be performed to estimate the DoR curve for each arm.

10.3.1.3. Overall Survival

Overall survival is defined as the time from randomization until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the

last date the patient is known to be alive. The first OS analysis will be at the time of the PFS analysis. The final analysis of OS will occur 24 months after the last patient enters treatment.

Overall survival will be compared between treatment arms using a stratified log-rank test, stratified by the randomization strata. The corresponding hazard ratio (HR) between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata. Overall survival curves, the median OS time, and survival rates at every 6 months up to 24 months for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958).

10.3.2. Safety Analyses

All patients who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity.

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI -CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event.

Both the CTCAE code and the AE verbatim text will be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 (or higher). Adverse events will be reported using a process which includes both CTCAE v4.0 and MedDRA:

- In CTCAE version 4.0, each CTCAE term is a MedDRA lower level term (LLT), except in the case where the CTCAE term is a MedDRA System Organ Class (SOC) followed by 'Other – specify'.
- The CTCAE v4.0 term reported by the investigator will be mapped to the MedDRA Preferred Term (PT) and SOC of the corresponding MedDRA LLT, unless the reported CTCAE term is 'Other – specify'.
- If the reported CTCAE term is 'Other – specify', the MedDRA LLT, PT, and SOC mapped from the verbatim AE term will be used.
- All listings and summaries will use the PT resulting from this process. The LLT will be used in the treatment-emergent computation.

The following safety analyses will be based on the safety population. Safety analyses will be conducted by treatment arm and will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- SAEs, including possible relationship to study drug
- AEs leading to dose adjustments
- discontinuations from study treatment due to AEs or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs
- extent of exposure

10.3.3. Other Analyses

10.3.3.1. Patient Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as reasons for discontinuation from study treatment and reasons for discontinuation from study. A summary of all important protocol deviations will be provided.

10.3.3.2. Patient Characteristics

Patient characteristics at baseline will be summarized by treatment arm:

- Patient demographics
- Baseline disease characteristics
- Historical illnesses
- Prior anticancer therapy

Other patient characteristics will be summarized as deemed appropriate

10.3.3.3. Concomitant Therapy

A summary of prior and concomitant medications by treatment arm will be reported.

10.3.3.4. Poststudy-Treatment-Discontinuation Therapy

The numbers and percentages of patients receiving poststudy-treatment-discontinuation anticancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug class and/or name, overall and by line of therapy.

10.3.3.5. Treatment Compliance

The number of cycles received, dose omissions, dose reductions, dose intensity, and treatment compliance will be summarized for all treated patients by treatment arm.

The actual cumulative dose taken will be determined based on counting the number of capsules returned at each visit and subtracting that number from the number of capsules dispensed. The expected cumulative dose to be taken will be determined based on the assigned dose and taking into account any dose reductions or omissions. Treatment compliance will be measured as a percentage of the actual cumulative dose divided by the expected cumulative dose.

10.3.3.6. Pharmacokinetic/Pharmacodynamic Analyses

PK analyses will be conducted on all patients who have received at least 1 dose of abemaciclib and have evaluable PK samples and sufficient dosing information.

Mean population PK parameters for abemaciclib in plasma (for example, clearance, exposure, volume of distribution,) and inter-individual PK variability will be computed using nonlinear mixed effect modelling (NONMEM).

Likewise, and if warranted by the data, mean population PK parameters for tamoxifen and endoxifen in plasma and interindividual variability estimates will also be computed using nonlinear mixed-effect modelling implemented in NONMEM.

The observed concentrations of abemaciclib, tamoxifen, and their respective metabolites may be summarized by time and dose.

PD samples will be collected as specified in the Study Schedule and PK and PD Sampling Schedule (cross reference). Refer to these attachments (including footnotes) for important information about these samples and their collection.

Furthermore, PD data (such as neutrophil, lymphocyte, or platelet counts in blood) collected in this study may also be analyzed by means of NONMEM and connected to the population PK model in a PK/PD model.

PD data from all patients undergoing PD assessments will be analyzed. The PD data will be combined and exploratory analyses will be conducted to determine if a relationship exists between plasma concentration and PD effect(s) in humans. Interpatient variability in human PD response may also be assessed.

10.3.3.7. Biomarker Analyses

Biomarker analyses will be based on the subset of patients from the above cohorts from whom a valid assay result (according to laboratory guideline) has been obtained. Exploratory correlative analyses will be performed to investigate associations between biomarkers and clinical endpoints as deemed appropriate.

10.3.3.8. Health Outcome/Quality of Life Analyses

Patient-reported outcomes are measured through paper versions of the following:

- mBPI-sf (modified Brief Pain Inventory, Short Form)
- EORTC QLQ-C30 (The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30)

Descriptive statistics will be calculated for patient-reported data for each instrument. Comparisons between arms will be made for pain, pain interference, functional scales (physical, role, emotional, cognitive, and social), other disease symptoms, health status, and overall quality of life. The number of missing and incomplete questionnaires/assessments by visit will be summarized for each instrument, including the reason not completed.

Exploratory analysis may be performed to investigate associations between patient-reported data (mBPI-sf and EORTC QLQ-C30) and additional clinical efficacy and/or utilization measures as appropriate.

Further analysis details will be described in the SAP.

10.3.3.9. Healthcare Resource Utilization

Utilization data overall and by study treatment arm will be summarized descriptively by category (for example, transfusions and hospitalization days) as appropriate.

Exploratory analyses may be performed to investigate associations between the utilization data and the clinical endpoints.

10.3.4. Subgroup Analyses

A prespecified list of subgroups will be identified in the SAP. The treatment effect within each subgroup will be summarized. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics, for example, prognostic significance.

10.3.5. Interim Analyses

There are no planned interim analyses.

11. References

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, Kaasa S, Klee MC, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw KCA, Sullivan M, Takeda F. The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365-376.

[ACS] American Cancer Society. Sarcoma: adult soft tissue cancer. 2015. Available from URL: http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf. Accessed on February 1, 2016.

Asghar U, Witkiewwicz AK, Turner NC, Knudsen ES. The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nat Rev Drug Discov.* 2015;14(2):130-146.

Cardoso F, Costa A, Norton L, Cameron D, Cufer T, Fallowfield L, Francis P, Gligorov J, Kyriakides S, Lin N, Pagani O, Senkus E, Thomssen C, Aapro M, Bergh J, Di Leo A, El Saghir N, Ganz PA, Gelmon K, Goldhirsch A, Harbeck N, Houssami N, Hudis C, Kaufman B, Leadbeater M, Mayer M, Rodger A, Rugo H, Sacchini V, Sledge G, van't Veer L, Viale G, Krop I, Winer E. 1st International consensus guidelines for advanced breast cancer (ABC 1). *Breast.* 2012;21(3):242-252.

Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore.* 1994;23(2):129-138.

Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, Chollet P, Manikas A, Diéras V, Delozier T, Vladimirov V, Cardoso F, Koh H, Bougnoux P, Dutcus CE, Seegobin S, Mir D, Meneses N, Wanders J, Twelves C; EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) investigators. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomized study. *Lancet.* 2011;377(9769):914-923.

Cox DR. Regression models and life-tables. *J Royal Stat Soc Ser B.* 1972;74(2):187-220.

Eisenhauer EA, Therasse P, Bogaert J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):E359-386.

Goetz MP, Beeram M, Beck T, Conlin AK, Dees EC, Dickler MN, Helsten TL, Conkling PR, Edenfield WJ, Richards DA, Turner PK, Cai N, Chan EM, Pant S, Becerra CH, Kalinsky K, Puhalla SL, Rexer BN, Burris HA, Tolaney SM. Abemaciclib, an inhibitor of CDK4 and CDK6, combined with endocrine and HER2-targeted therapies for women with metastatic breast cancer. [P4-13-25]. Poster presented at: San Antonio Breast Cancer Symposium; 11 December 2015; San Antonio, TX.

Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol.* 2010;28(16):2784-2795.

Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, Cronin KA. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst.* 2014;106(5).

Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2012. Bethesda, MD: National Cancer Institute. Available at: http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015. Accessed on February 1, 2016.

Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. *J Amer Stat Assoc*. 1958;53:457-481.

Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, Olivo MS, He Y, Dutcus CE, Cortes J. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol.* 2015;33(6):594-601.

Krop IE, Kim SB, González-Martín A, LoRusso PM, Ferrero JM, Smitt M, Yu R, Leung AC, Wildiers H; TH3RESA study collaborators. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014;15(7):689-699.

Malumbres M, Barbacid M. To cycle or not to cycle: a critical decision in cancer. *Nat Rev Cancer.* 2001;1(3):222-231.

Neuman E, Ladha MH, Lin N, Upton TM, Miller SJ, DiRenzo J, Pestell RG, Hinds PW, Dowdy SF, Brown M, Ewen ME. Cyclin D1 stimulation of estrogen receptor transcriptional activity independent of cdk4. *Mol Cell Biol.* 1997;17(9):5338-5347.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol.* 1982;5:649-655.

Ortega S, Malumbres M, Barbacid M. Cyclin-D dependent kinases, INK4 inhibitors and cancer. *Biochim Biophys Acta*. 2002;1602:73-87.

O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, Fumoleau P, Jones S, Lui WY, Mauriac L, Twelves C, Van Hazel G, Verma S, Leonard R. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol.* 2002;20(12):2812-2823.

Patnaik A, Rosen LS, Tolaney SM, Tolcher AW, Goldman JW, Gandhi L, Papadopoulos KP, Beeram M, Rasco DW, Myrand SP, Kulanthaivel P, Andrews JM, Frenzel M, Cronier D, Chan EM, Flaherty K, Wen PY, Shapiro G. LY2835219, a novel cell cycle inhibitor selective for CDK4/6, in combination with fulvestrant for patients with hormone receptor positive (HR+) metastatic breast cancer. *J Clin Oncol.* 2014;32(suppl):5s. Abstract 534.

Sherr CJ. Cancer cell cycles. *Science.* 1996;274:1672-1677.

Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO. Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Onc.* 2015. Available at: http://jco.ascopubs.org/content/early/2015/07/08/JCO.2015.62.3488.full. Accessed October 01, 2015.

Stearns V, Johnson MD, Rae JM, Morocho A, Novielli A, Bhargava P, Hayes DF, Desta Z, Flockhart DA. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst.* 2003;95(23):1758-1764.

Swallow E, Zhang J, Thomason D, Tan RD, Kageleiry A, Signorovitch J. Real-world patterns of endocrine therapy for metastatic hormone-receptor-positive (HR+)/human epidermal growth factor receptor-2-negative (HER2-) breast cancer patients in the United States: 2002-2012. *Curr Med Res Opin.* 2014;30(8):1537-1545.

Tate SC, Cai S, Ajamie RT, Burke T, Beckmann RP, Chan EM, De Dios A, Wishart GN, Gelbert LM, Cronier DM. Semi-mechanistic pharmacokinetic/pharmacodynamic modeling of the antitumor activity of LY2835219, a new cyclin-dependent kinase 4/6 inhibitor, in mice bearing human tumor xenografts. *Clin Cancer Res.* 2014;20:3763.

Tolaney SM, Beeram M, Beck JT, Conlin AK, Dees EC, Dickler MN, Helsten TL, Conkling PR, Edenfield WJ, Richards DA, Turner PK, Cai N, Chan EM, Pant S, Becerra CH, Kalinsky K, Puhalla SL, Rexer BN, Burris HA, Goetz MP. A phase Ib study of abemaciclib with therapies for metastatic breast cancer. *J Clin Oncol.* 2015;33(suppl). Abstract 522.

Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, Hanna W, Jenkins RB, Mangu PB, Paik S, Perez EA, Press MF, Spears PA, Vance GH, Viale G, Hayes DF. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol.* 2013;31(31):3997-4013.

Zwijsen RM, Buckle RS, Hijmans EM, Loomans CJ, Bernards R. Ligand-independent recruitment of steroid receptor coactivators to estrogen receptor by cyclin D1. *Genes Dev.* 1998;12(22):3488-3498.

Zwijsen RM, Wientjens E, Klompmaker R, van der Sman J, Bernards R, Michalides RJ. CDK-independent activation of estrogen receptor by cyclin D1. *Cell.* 1997;88(3):405-415.

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	Adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment.
CAP	College of American Pathologists
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
collection database	a computer database where clinical trial data are entered and validated.
CR	complete response
CRP	Clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DoR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.

EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ER	estrogen receptor
ERB/IRB	ethical review board/institutional review board
GCP	good clinical practice
HER2-	human epidermal growth factor receptor 2 negative
HIV	human immunodeficiency virus
HR	hazard ratio
HR+	hormone receptor positive
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
Interim analysis	An interim analysis is an analysis of clinical trial data conducted before the final reporting database is created/locked.
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IVRS/IWRS	interactive voice-response system/interactive web-response system
LLT	lower level term
mBC	metastatic breast cancer
mBPI-sf	modified Brief Pain Inventory-short form

MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	Preferred Term
Q12H	every 12 hours
QD	every day
randomize	the process of assigning patients to an experimental group on a random basis
RANK-L	receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SOC	System Organ Class
SUSARs	suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.

TBL	total bilirubin
ULN	upper limit of normal
VTE	venous thromboembolic event
women of child bearing potential (WOCBP)	Fertile, following menarche and until becoming postmenopausal, unless permanently sterile. Permanent sterilization includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Appendix 2. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in the study
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of study treatment.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

Ethical Review

Documentation of ERB/IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs/IRBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERBs/IRBs should be provided with the following:

- the current IB and updates during the course of the study
- the ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations.

Some obligations of Lilly may be assigned to a third-party organization.

Investigator Information

Licensed physicians specializing in oncology will participate as investigators in this clinical trial.

Protocol Signatures

Lilly's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The investigator will sign the final clinical study report for this study, indicating agreement, to the best of his or her knowledge, with the analyses, results, and conclusions of the report.

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

An investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The Lilly responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs/IRBs with direct access to original source documents.

Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into Lilly provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome (PRO) measures (for example, MDASI) or a participant diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB/IRB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology - central laboratory [a]	
Leukocytes (WBC)	Erythrocytes (RBC)
Neutrophils[b]	Hemoglobin (HGB)
Lymphocytes	Hematocrit (HCT)
Monocytes	Mean corpuscular volume (MCV)
Eosinophils	Mean corpuscular hemoglobin concentration (MCHC)
Basophils	Platelets (PLT)

Chemistry - central laboratory (except as indicated) [a]	
Serum Concentrations of:	
Alanine aminotransferase (ALT)	Calcium
Albumin	Chloride
Alkaline phosphatase	Creatinine
Aspartate aminotransferase (AST)	Potassium
Bilirubin, direct	Protein, total
Bilirubin, total (TBL)	Sodium
Blood urea nitrogen (BUN) or blood urea	Triglycerides (Arm A only)[c]

Renal panel - central laboratory

Cystatin-C

Pregnancy Test (for female patients of childbearing potential) - local laboratory

Serum pregnancy test [d]

Abbreviations: CRF = case report form; RBC = red blood cells; WBC = white blood cells.

[a] Treatment decisions may be based on local laboratory results.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should reported together.

[c] Arm A only. Triglycerides will be evaluated every other cycle starting with Cycle 2 until Cycle 6, and then every third cycle thereafter until treatment discontinuation.

[d] Additional serum pregnancy tests may be performed locally, on Day 1 (or up to 3 days before Day 1) of every cycle beginning with Cycle 2 and at short term follow up for women of child bearing potential if mandated by local country regulations.

Appendix 4. Sampling Schedule for Genetics/ Biomarkers/ Pharmacokinetics/ Pharmacodynamics

It is essential that the exact time of dose administration is recorded. The exact time of collection of each venous blood sample will be based on the time of study drug administration.

Pharmacokinetic sampling windows are provided as guidance. Due to practical and logistical concerns, some deviation from the specified sampling time is normal and expected. Sites should keep in mind that drawing the sample and recording the actual time on the appropriate form is of primary importance. Differences from the time specified in the protocol are not considered protocol deviations as long as samples are collected and accurate dates and times are recorded in a timely manner on the appropriate forms.

Sampling Schedule for Genetics/Biomarkers/ Pharmacokinetics/Pharmacodynamics

Procedure	Baseline/Cycle 1	Cycle 2	Cycle 3	Short-Term Follow up
Pharmacokinetics[a]	C1D1: any time after abemaciclib dosing C1D15: any time after abemaciclib dosing	C2D1: any time after abemaciclib dosing C2D15: any time after abemaciclib dosing	C3D1: any time after abemaciclib dosing	
Archived Tumor tissue[b]	Obtain archived tumor block or cut unstained positively charged slides after eligibility is confirmed.			
Plasma (Biomarker)	C1D1: before dosing of abemaciclib	C2D1: any time before dosing of abemaciclib	C3D1: any time before dosing of abemaciclib	Collect at time of discontinuation
Whole blood (Pharmacogenetics)[c]	C1D1: any time before or after abemaciclib dosing			

Abbreviations: C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; C2D1 = Cycle 2 Day 1; C2D15 = Cycle 2 Day 15; C3D 1 = Cycle 3 Day 1; h = hour.

a Whole blood (2 mL) will be collected to determine concentrations of abemaciclib and its metabolites. A separate 2 mL whole blood will be collected to determine concentrations of tamoxifen and its metabolite endoxifen. All PK samples should be taken anytime after the AM dose.

b Collection of archived tumor tissue is required if available. Previously archived formalin-fixed paraffin-embedded tumor tissue obtained from the primary tumor or metastatic site should be provided as a whole block or unstained slides.

c A pretreatment blood sample is preferred; however, the whole blood sample for genetic analysis may be collected at a later time point if necessary.

Appendix 5. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin (TBL)	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase (ALT)	**Recommended Autoimmune Serology:**
Aspartate aminotransferase (AST)	Anti-nuclear antibody[a]
Gamma-glutamyl transferase (GGT)	Anti-smooth muscle antibody[a]
Creatine phosphokinase (CPK)	Anti actin antibody[a]

Abbreviations: CRF = case report form; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[c] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 6. Protocol JPCG Inducers, Strong Inhibitors of CYP3A or Substrates of CYPS with Narrow Therapeutic Range

The information in this attachment is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Inducers of CYP3A
Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St. John's wort

[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

Strong inhibitors of CYP3A
Aprepitant
Ciprofloxacin
Clarithromycin
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Verapamil

Cytochrome P450 Substrates with Narrow Therapeutic Range	
Cytochrome P450	**Substrate**
CYP1A2	Theophylline Tizanidine
CYP2C9	Warfarin Phenytoin
CYP2D6	Thioridazine Pimozide
CYP3A	Alfentanil Astemizole Cisapride Cyclosporine Dihydroergotamine Ergotamine Fentanyl Pimozide Quinidine Sirolimus Tacrolimus Terfenadine

Appendix 7. Protocol JPCG CTCAE 4.03 Diarrhea Definition

Diarrhea will be evaluated in this study using the criteria proposed by Common Terminology Criteria for Adverse Events (CTCAE) v4.0 revised: CTCAE 4.03–June 14, 2010: Gastrointestinal disorders.

Gastrointestinal Disorders					
Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >= 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterized by frequent and watery bowel movements					

Abbreviation: ADL = Activities of Daily Living

Appendix 8. Protocol JPCG RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone Lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the case record form (CRF) in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual

lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10 mm short axis).

Non-CR/ non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Appendix 9. Protocol JPCG: ECOG Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead.

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

Appendix 10. Protocol Amendment I3Y-MC-JPCG(b) Summary
A Randomized, Open-Label, Phase 2 Study of Abemaciclib plus Tamoxifen or Abemaciclib Alone, in Women with Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer

Overview

Protocol I3Y-MC-JPCG (A Randomized, Open-Label, Phase 2 Study of Abemaciclib plus Tamoxifen or Abemaciclib Alone, in Women with Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer) has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes for the changes made to this protocol are as follows:

- Section 6.1 modified inclusion criterion [8] contraceptive method period
- Section 7.4.1.1, Table JPCG.7. modified along with Sections 9.4.2.1, 9.4.2.2 and 9.4.2.3 for alignment with safety monitoring information for hepatic conditions, renal function and VTEs.
- Appendix 1 included TBL and VTE in abbreviations
- Appendix 6 CYPs text updated to align with abemaciclib program information.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Section 6.1 Inclusion Criteria

[8] Women of childbearing potential must have a negative serum pregnancy test at baseline (within 7 days prior to Cycle 1 Day 1), and agree to use a highly effective non-hormonal contraceptive method during the treatment period and for 3 ~~months~~ weeks following the last dose of abemaciclib~~the study drug~~. This amount of time may be longer depending on the other treatments received during this trial.

Section 7.4.1 Special Treatment Considerations

Table JPCG.7. Toxicity Dose Adjustments and Delays of Abemaciclib

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity Section 7.4.1.1.2.1	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Hematologic Toxicity Section 7.4.1.1.2.1	Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity Section 7.4.1.1.2.1	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic toxicity: ~~Patient~~If patient requires administration of blood cell growth factors. Section 7.4.1.1.2.1 and 7.7.2	Regardless of severity. (~~Growth factors u~~Use of growth factors according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2	Dose **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that led to the use of growth factor
Nonhematologic Toxicity[b] (except diarrhea and ALT increased) Section 7.4.1.1.2.1	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose ~~**MAY**~~ **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose ~~**MAY**~~ **MUST** be reduced by 1 dose level~~investigator's discretion~~.
Nonhematologic Toxicity Section 7.4.1.1.2.1	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 7.7.1.1	Grade 2 that does not resolve within 24 hours to at least Grade 1~~Requires hospitalization or Grade 3 or 4~~	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose reduction is NOT required.~~**MUST be reduced by 1 dose level**~~
Diarrhea Section 7.7.1.1	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures or any Grade of diarrhea that requires hospitalization~~within 24 hours to at least Grade 1~~	Dose ~~**SHOULD**~~ **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose ~~**MAY**~~ **MUST** be reduced by 1 dose level ~~investigator's discretion~~.
Diarrhea Section 7.7.1.1	Grade 3 or 4~~Diarrhea recurs despite maximal supportive measures after resuming same dose level after~~	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.

	~~initial Grade 2 diarrhea~~		
ALT Increased Section 9.4.2.1	Persistent or recurrent[a] Grade 2 (>3.0-5.0×ULN), or Grade 3 (>5.0-20.0×ULN)[c]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT Increased Section 9.4.2.1	Grade 4 (>20.0×ULN)	Abemaciclib therapy **MUST** be discontinued.	Abemaciclib therapy **MUST** be discontinued.
ALT Increased with increased total bilirubin, in the absence of cholestasis	Grade 3 increased ALT (>5.0 x ULN) with total bilirubin >2 x ULN	Abemaciclib therapy MUST be discontinued	Abemaciclib therapy MUST be discontinued

Abbreviation: ALT = alanine transaminase; ASCO = American Society of Clinical Oncology.

Note: ~~MAY = per the investigator's clinical judgment; SHOULD = not mandatory but highly recommended;~~MUST = mandatory.

a Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).~~Recurrent in the context of dose interruptions and delays refers to the same event occurring within the next 8 weeks (as measured from the stop date of the first event). This does not include events in the same class (for example, neutropenia followed by anemia 1 month later).~~As a general ~~approach~~guidance, based on the risk/benefit balance assessment per the investigator~~:~~ ~~F~~, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose if the patient satisfies the following conditions:

- ~~The patient showed~~shows stable hematological counts (≤Grade 2) during that timeframe
- ~~In the~~has absence of any infectious sign or risk factor
- ~~The patient~~ is getting benefit from study treatment

b Additional guidance for renal and hepatic monitoring is in Section 9.4.2.

c Grade 3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 9.4.2.1 for additional guidance for hepatic monitoring

Section 9.4.2.1 Special Hepatic Safety Data Collection

If a study patient experiences elevated alanine aminotransferase (ALT) ≥5-fold the upper limit of normal (ULN) and elevated total bilirubin (TBL) ≥2-fold ULN, or ALT >8x ULN for patients with underlying baseline hepatic metastases, liver tests (Appendix 5), including ALT, AST, TBL, direct bilirubin, gamma glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (Appendix 5) and in consultation with the Lilly CRP. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels. Additional diagnostic testing should be considered to rule out cause of increased liver enzymes per the investigator's discretion.

Hepatic monitoring tests (Appendix 5) should be collected in the event that 1 or more of the following conditions is met for the patient during the course of the study:

- ALT ≥5×ULN and TBL ≥2×ULN
- ALT>8x ULN for patients with underlying hepatic metastasis

- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests

~~clinical and laboratory monitoring should be initiated by the investigator.~~

~~Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See~~ Appendix 5~~.~~

Section 9.4.2.2. Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C calculated glomerular filtration rate. Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function. See Appendix 3. ~~Dose alterations (omission, reduction, and discontinuation) should not solely be based on interpretations of serum creatinine values because they may not reflect renal function.~~

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities (Table JPCG.7).

Section 9.4.2.3. Venous Thromboembolic Events

In the randomized Phase 3 studies in breast cancer patients who received abemaciclib in combination with endocrine therapy, there was a greater number of patients who experienced venous thromboembolic events (VTEs) in the abemaciclib plus endocrine therapy arm than in the placebo plus endocrine therapy arm. The majority of the events were non-serious and were treated with low-molecular-weight heparin. Generally, these events did not result in discontinuation of the study treatment. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. For suspected or confirmed VTE (eg. deep vein thrombosis or pulmonary embolism), treatment should occur according to usual clinical practice.

Appendix 1. Abbreviations and Definitions…

TBL	total bilirubin
…	
VTE	venous thromboembolic event
…	

Appendix 6. Protocol JPCG Inducers, Strong Inhibitors of CYP3A or Substrates of CYPS with Narrow Therapeutic Range…

Strong inhibitors of CYP3A	
~~All HIV protease inhibitors~~	
Aprepitant	
Ciprofloxacin	
Clarithromycin	
Diltiazem	
Erythromycin	
Fluconazole	
Itraconazole	
Ketoconazole	
Nefazodone	
Verapamil	
Cytochrome P450 Substrates with Narrow Therapeutic Range	
Cytochrome P450	**Substrate**
CYP1A2	Theophylline Tizanidine
~~CYP2C8~~	~~Paclitaxel~~

…

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